THE INDISPENSABLE POCKET GUIDE FOR ALL THOSE WORKING IN MICROBIOLOGY AND INFECTIOUS DISEASE

OXFORD HANDBOOK OF INFECTIOUS DISEASES AND MICROBIOLOGY

Estée Török | Ed Moran | Fiona Cooke

A systematic overview of clinical microbiology, plus detailed descriptions of diseases and conditions

Up-to-date with the most recent advances, legislation and 'hot topics', including bioterrorism

Includes new topics such as specimen collection, commonly used media, molecular diagnostics, and antimicrobials in pregnancy

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Oxford Handbook of Infectious Diseases and Microbiology

Second edition

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Foreword to the second edition

It is a great honour to be writing the foreword for the latest edition of the *Oxford Handbook Infectious Diseases and Microbiology*.

It is put together by a talented and committed group of authors who have direct experience and insight on the practicalities of delivering specialist clinical care in infectious diseases and microbiology, as well as in running expert laboratory support and advancing research in the field.

The latest edition of the Handbook provides an ideal and useful combination of being organized into chapters that are both organism-based and syndrome-based. The new edition importantly provides more information and detail on infection prevention which is increasingly important in the context of addressing antimicrobial resistance as well as protecting our patients and staff. Well laid out, user-friendly flow charts have been provided in this edition providing valuable rapid resources, for example in organism identification. A newly updated section on antibiotic resistance and antibiotic agents also provides critical information for the now combined ID/Microbiology trainees in the UK, but also valuable for any infection specialty trainees internationally.

It is marvellous to see that the Handbook is promoting cross-disciplinary working and provides a shared resource for all of those working in infectious diseases and clinical microbiology, whether they are students, trainees or senior doctors or ID pharmacists, nurses and biomedical scientists, infection nurses.

Alison Holmes,
Professor of Infectious Diseases,
Imperial College, UK

Preface to the second edition

Medicine is all about adapting to change as research is published and new therapies launched. In the years since the publication of the first edition of this book the treatment of viral hepatitis has transformed beyond recognition, to the extent that drugs have been introduced *and* withdrawn as obsolete, and novel classes of anti-virals and antibiotics are now mainstream. Those of us working in infection have additional challenges: the rise of entirely new diseases (MERS, Ebola, Chikungunya and Zika have each taken their turn in the spotlight), the failure of treatments that have served us faithfully for many years (multi-resistant organisms now attract the attention of Presidents and Prime Ministers), and the automation and molecular revolution in our diagnostic laboratories. UK infection training has responded with the distinction between classic 'Infectious Disease' and 'Microbiology' becoming ever harder to spot, recognized with the launch of Core Infection Training.

Whilst as ever no single book—or at least no single portable book—can tell you everything you need to know, we hope that this second edition of the *Oxford Handbook of Infectious Diseases and Microbiology* will continue to prompt, guide, and educate those caring for people with infections.

Estée Török,
Ed Moran, Fiona Cooke

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Contents

Symbols and abbreviations

A–a	alveolar–arterial
ABC HSR	abacavir hypersensitivity reaction
ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ABPI	ankle–brachial pressure index
ACA	acrodermatitis chronica atrophicans
ACDP	Advisory Committee on Dangerous Pathogens
ACE	angiotensin-converting enzyme
ACT	artemisinin combination therapy; adenylate cyclase toxin
ADH	antidiuretic hormone
ADL	acute adenolymphangitis
AFB	acid-fast bacilli
AFLP	amplified fragment length polymorphism
AIDS	acquired immune deficiency syndrome
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AME	aminoglycoside-modifying enzyme
AMP	adenosine monophosphate
AMRHAI	Antimicrobial Resistance and Healthcare Associated Infections Reference Unit
a.m.	*ante meridiem* (before noon)
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
aP	acellular pertussis (vaccine)
APACHE	acute physiology and chronic health evaluation (score)
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ART	antiretroviral therapy
ASD	atrial septal defect
ASOT	anti-streptolysin O titre
AST	aspartate transaminase
ATL	adult T-cell leukaemia/lymphoma

ATN	antiretroviral toxic neuropathy
ATP	adenosine triphosphate
AUC	area under the curve
AV	atrioventricular
BA	blood agar; bacillary angiomatosis
BAL	bronchoalveolar lavage
BC	blood culture
BCG	bacillus Calmette–Guérin
BCYE	buffered charcoal yeast extract
bd	twice daily
BHIVA	British HIV Association
BIA	British Infection Association
BKV	BK virus
BLNAR	β-lactamase-negative ampicillin-resistant
BMT	bone marrow transplant/ation
BNF	*British National Formulary*
bp	base pair
BP	bacterial peliosis
BSAC	British Society for Antimicrobial Chemotherapy
BSE	bovine spongiform encephalopathy
BSI	bloodstream infection
BTS	British Thoracic Society
BV	bacterial vaginosis
Ca	calcium
cAMP	cyclic adenosine monophosphate
CA-MRSA	community-acquired meticillin-resistant *Staphylococcus aureus*
CAP	community-acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CATT	card agglutination tests for *Trypanosoma gambiense* trypanosomes
CBD	common bile duct
CCDC	Consultant in Communicable Disease Control
CCEY	cefoxitin cycloserine egg yolk
CCF	congestive cardiac failure
CCFA	cefoxitin cycloserine fructose agar
CCHF	Congo–Crimean haemorrhagic fever
ccr	cassette chromosome recombinase

CCU	clean-catch urine
CDAD	*Clostridium difficile*-associated disease/diarrhoea
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
cDNA	complementary deoxyribonucleic acid
CDRN	*Clostridium difficile* Ribotyping Network
CDSC	Communicable Disease Surveillance Centre
CE	California encephalitis
CEE	central European encephalitis
CF	cystic fibrosis
CFA	colonization factor antigen; circulating filarial antigen
CFTs	complement fixation tests
CFTR	cystic fibrosis transmembrane conductance regulator
cfu	colony-forming unit
CIN	Cefsulodin, Irgasan, Novobiocin; cervical intraepithelial neoplasia
CIS	Commonwealth of Independent States
CJD	Creutzfeldt–Jakob disease
CK	creatine kinase
CKD	chronic kidney disease
Cl^-	chloride ion
CL	containment level
CLED	cystine, lactose, electrolyte-deficient (agar)
CLSI	Clinical & Laboratory Standards Institute
cm	centimetre
CMI	cell-mediated immunity
CMV	cytomegalovirus
CNA	colistin nalidixic acid agar
CNS	central nervous system
CO_2	carbon dioxide
CoNS	coagulase-negative staphylococci
COPD	chronic obstructive pulmonary disease
COSHH	Control of Substances Hazardous to Health
CPA	Clinical Pathology Accreditation
CPE	carbapenemase-producing *Enterobacteriaceae*
CPK	creatine phosphokinase
CQC	Care Quality Commission

CT-BSI	catheter-related bloodstream infection
CrCl	creatinine clearance
CRE	carbapenem-resistant *Enterobacteriaceae*
CRF	circulating recombinant form
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSSD	Centre for Surgical Sterilization and Disinfection
CSU	catheter specimen for urine
CT	computerized tomography
CVC	central venous catheter
CVID	common variable immunodeficiency
CVS	cardiovascular system
CXR	chest X-ray
DAA	direct-acting antiviral
DAIR	debridement and implant retention
DAT	direct agglutination test
DDT	dichlorodiphenyltrichloroethane
DEC	diethylcarbamazine
DEET	diethyltoluamide
DF	dengue fever
DFA	direct fluorescent antibody test
DH	Department of Health
DHF	dengue haemorrhagic fever
DHFR	dihydrofolate reductase
DHHS	Department of Health and Human Services
DHP-1	dehydropeptidase-1
DHPS	dihydropteroate synthase
DIC	disseminated intravascular coagulation
DIPC	Director of Infection Prevention and Control
DKA	diabetic ketoacidosis
dL	decilitre
DLA	acute dermatolymphangioadenitis
DMSA	dimercaptosuccinic acid (scan)
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
DNT	dermonecrotic toxin
DoH	Department of Health

dsDNA	double-stranded deoxyribonucleic acid
DSN	distal sensory neuropathy
DSP	dry sterilization process
DST	drug susceptibility testing
DTP	diphtheria, tetanus, polio (vaccine)
DVT	deep venous thrombosis
EASL	European Association for the Study of the Liver
EBNA	Epstein–Barr virus nuclear antigen
EBV	Epstein–Barr virus
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EEE	eastern equine encephalitis
EEG	electroencephalography
EF	(o)edema factor
eGFR	estimated glomerular filtration rate
EI	erythema infectiosum
EIA	enzyme-linked immunoassay
EIEC	enteroinvasive *Escherichia coli*
EITB	enzyme-linked immunoelectrotransfer blot
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy; erythema chronicum migrans
EMG	electromyography
EMJH	Ellinghausen-McCullough-Johnson-Harris
ENT	ear, nose, and throat
EO	ethylene oxide
epo	erythropoietin
EPP	exposure-prone procedure
EQA	external quality assessment
ERCP	endoscopic retrograde cholangiopancreatography
ESBL	extended-spectrum β-lactamase
ESCAPPM	*Enterobacter* spp., *Serratia* spp., *Citrobacter freundii*, *Acinetobacter* spp., *Proteus vulgaris*, *Providencia* spp., *Morganella morganii*
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ET	exfoliative toxin
ETEC	enterotoxigenic *Escherichia coli*

EUCAST	European Committee on Antimicrobial Susceptibility Testing
EVD	external ventricular drain
FAN	Fastidious Antibiotic Neutralization (bottle)
FAT	fluorescent antibody test
FBC	full blood count
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FEV_1	forced expiratory volume in 1 second
FFI	fatal familial insomnia
FHA	filamentous haemagglutinin
FNA	fine-needle aspiration
FTA-ABS	fluorescent treponemal antibody absorption (test)
FUO	fever of unknown origin
g	gram
G6PD	glucose-6-phosphate dehydrogenase
GAM	granulomatous amoebic encephalitis
GAS	group A *Streptococcus*
GBS	group B *Streptococcus*; Guillain–Barré syndrome
GBV-C	GB virus type C
GCS	Glasgow coma scale
G-CSF	granulocyte-colony-stimulating factor
GDH	glutamate dehydrogenase
GDP	guanosine diphosphate
geq	genome equivalent
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GISA	glycopeptide-intermediate *Staphylococcus aureus*
GMC	General Medical Council
GMP	good manufacturing practice
GNR	Gram-negative rod
GORD	gastro-oesophageal reflux disease
GP	general practitioner
GRE	glycopeptide-resistant *Enterococcus*
GSS	Gerstmann–Sträussler–Scheinker (disease)
GU	genitourinary

GUM	genitourinary medicine
GVHD	graft-versus-host disease
h	hour
HA	haemagglutinin
HAART	highly active antiretroviral therapy
HACCP	hazard analysis and critical control point
HAD	HIV-associated dementia
HAI	hospital-acquired infection
HA-MRSA	health care-acquired meticillin-resistant *Staphylococcus aureus*
HAP	hospital-acquired pneumonia
HAT	human African trypanosomiasis
HAV	hepatitis A virus
Hb	haemoglobin
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCAI	health care-associated infection
HCC	hepatocellular carcinoma
HCO_3^-	bicarbonate ion
HCoV	human coronavirus
HCV	hepatitis C virus
HCW	health-care worker
HDV	hepatitis D virus
H&E	haematoxylin and eosin (staining)
HE	Hektoen enteric
HELLP	haemolysis, elevated liver enzymes, low platelets (syndrome)
HEPA	high-efficiency particulate air
HEV	hepatitis E virus
HFM	hand, foot, and mouth (disease)
Hfr	high-frequency recombination
HHV	human herpesvirus
Hib	*Haemophilus influenzae* type b (vaccine)
HICPAC	Healthcare Infection Control Practices Advisory Committee

HIDA	hepatobiliary iminodiacetic acid
HII	High Impact Intervention: from 'Saving Lives' programme
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HLA	human leucocyte antigen
HNIG	human normal immunoglobulin
H_2O_2	hydrogen peroxide
HPA	Health Protection Agency
HPLC	high-pressure liquid chromatography
HPU	health protection unit
HPV	human papillomavirus
H_2S	hydrogen sulfide
HSE	Health and Safety Executive
HSP	Henoch–Schönlein purpura
HSV	herpes simplex virus
HTLV	human T-cell lymphotropic virus
HTM	health technical memorandum
HUS	haemolytic uraemic syndrome
IAS-USA	International Antiviral Society-USA
IBD	inflammatory bowel disease
ICC	infection control committee
ICD	infection control doctor
ICN	infection control nurse
ICP	intracranial pressure
ICT	infection control team
ICU	intensive care unit
ID	infectious diseases; implanted device
IDSA	Infectious Diseases Society of America
IDU	injecting drug user
IE	infective endocarditis
IFA	immunofluorescence assay/indirect fluorescent antibody
IFAT	immunofluorescence antibody test
IFN	interferon
Ig	immunoglobulin (IgA, IgE, IgG, IgM)
IGRA	interferon gamma release assay
IL	interleukin
IM	intramuscular

IMS	industrial methylated spirit
INH	inhaled
INR	international normalized ratio
IPV	inactivated polio vaccine
IQA	internal quality assurance
IQC	internal quality control
IRIS	immune reconstitution inflammatory syndrome
IS	insertion sequence
ISAGA	IgM immunosorbent agglutination assay
ITP	idiopathic thrombocytopenic purpura
IU	international unit
IUCD	intrauterine contraceptive device
IUGR	intrauterine growth restriction
IV	intravenously
IVC	intravascular catheter
IVIG	intravenous immunoglobulin
JCV	JC virus
JE	Japanese encephalitis
K	potassium
kb	kilobase
kg	kilogram
KOH	potassium hydroxide
kPa	kilopascal
KPC	*Klebsiella pneumoniae* carbapenemase
KS	Kaposi's sarcoma
L	litre
LAM	lipoarabinomannan
LAME	*Listeria*, 'atypical' organisms (*Mycoplasma, Chlamydia*), MRSA and enterococci
LCMV	lymphocytic choriomeningitis virus
LDH	lactate dehydrogenase
LES	Liverpool epidemic strain
LF	lethal factor
LFT	liver function test
LGV	lymphogranuloma venereum
LOS	lipo-oligosaccharide
LP	lumbar puncture

LPS	lipopolysaccharide
LRTI	lower respiratory tract infection
LTR	long tandem repeat
LTS	long-term storage
LVF	left ventricular failure
m	metre
MAC	*Mycobacterium avium* complex
MAI	*Mycobacterium avium intracellulare*
MALDI-TOF	matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy
MALT	mucosa-associated lymphoid tissue
MAT	micro-agglutination test
MBC	minimum bactericidal concentration
MBL	metallo-β-lactamases
MC&S	microscopy, culture, and sensitivity
MCD	multicentric Castleman's disease; mild neurocognitive disorder
MDI	microbiological documented infection
MDR	multidrug-resistant
MDRD	modification of diet in renal disease
MDT	multidrug therapy
MEC	minimum effective concentration
mg	milligram
Mg	magnesium
MGE	mobile genetic element
MGIT	Mycobacteria Growth Indicator Tube
MHC	major histocompatibility complex
MIC	minimum inhibitory concentration
MIF	micro-immunofluorescent antibody
min	minute
mL	millilitre
MLEE	multilocus enzyme electrophoresis
MLS_B	macrolide-lincosamide-streptogramin B (resistance)
MLST	multiple locus sequence typing
MLVA	multiple loci variable number repeat tandem analysis
mm	millimetre
mmHg	millimetre of mercury

mmol	millimole
MMR	measles, mumps, rubella (vaccination)
MODS	multiple organ dysfunction syndrome
MOTT	mycobacteria other than tuberculosis
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRSA	meticillin-resistant *Staphylococcus aureus*
MSA	mannitol salt agar
MSCRAMM	microbial surface components recognizing adhesive matrix molecule
MSM	men who have sex with men
MSSA	meticillin-sensitive *Staphylococcus aureus*
MSU	midstream urine
MTB	*Mycobacterium tuberculosis*
NA	neuraminidase
NAAT	nucleic acid amplification test
NaCl	sodium chloride
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate oxidase
NASBA	nucleic acid sequence-based amplification
NASH	non-alcoholic steatohepatitis
ND	notifiable disease
NDM	New Delhi metallo-β-lactamase-1
neb	nebulized
NG	nasogastric
NGS	next-generation sequencing
NH_4^+	ammonium ions
NHL	non-Hodgkin's lymphoma
NHSBT	NHS Blood and Transplant (Tissue Services)
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
NINSS	Nosocomial Infection National Surveillance Scheme (UK)
NK	natural killer
nm	nanometre
NNRTI	non-nucleoside reverse transcriptase inhibitor

NPA	nasopharyngeal aspirate
NRTI	nucleoside/nucleotide analogue reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NTM	non-tuberculous mycobacteria
NTS	non-typhoidal *Salmonella* species
NYC	New York City (agar)
NVS	nutritionally variant streptococci
OCP	oral contraceptive pill
od	once a day
OHS	oral hydration salts
OLM	ocular larva migrans
OMP	outer membrane protein
ONPG	*o*-nitrophenyl-B-*D*-galactopyranoside
OPAT	outpatient antimicrobial therapy
OPSI	overwhelming post-splenectomy infection
OPV	oral polio vaccine
ORF	open reading frame
PA	protective antigen
PABA	para-aminobenzoic acid
PAE	post-antibiotic effect
PaO_2	partial pressure of arterial oxygen
PAS	para-aminosalicylic acid
PAS	periodic acid–Schiff (staining)
PBMC	peripheral blood mononuclear cell
PBP	penicillin-binding protein
PCNSL	primary central nervous system lymphoma
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PD	peritoneal dialysis
PDA	patent ductus arteriosus
PDH	progressive disseminated histoplasmosis
PE	pulmonary embolism
PEA	phenyl ethanol agar
PEG-IFN	pegylated interferon
PEL	primary effusion lymphoma

PEP	post-exposure prophylaxis
PEPSE	post-exposure prophylaxis following sexual exposure
PfEMP1	*Plasmodium falciparum*-infected erythrocyte membrane protein 1
PFGE	pulsed-field gel electrophoresis
PGL	persistent generalized lymphadenopathy
PHE	Public Health England
PI	protease inhibitor
PIA	polysaccharide intracellular adhesion
PICC	peripherally inserted central catheter
PICU	paediatric intensive care unit
PID	pelvic inflammatory disease
PII	period of increased incidence
PJI	prosthetic joint infection
p.m.	*post meridiem* (after noon)
PML	progressive multifocal leukoencephalopathy
PO	orally
PPD	purified protein derivative
PPE	personal protective equipment
PPI	proton pump inhibitor
ppm	part per million
PR	per rectum
PRCA	pure red cell aplasia
PrEP	pre-exposure prophylaxis
PROM	premature rupture of the membranes
PrP	prion protein
PSA	prostate-specific antigen
PSS	post-splenectomy sepsis
PT	prothrombin time; pertussis toxin
PTC	percutaneous transhepatic cholangiography
PTLD	post-transplant lymphoproliferative disorder
PUO	pyrexia of unknown origin
PV	per vagina
PVC	peripheral venous catheter
PVE	prosthetic valve endocarditis
PVL	Panton–Valentine leucocidin
QAC	quaternary ammonium compound

qds	four times a day
qPCR	quantitative polymerase chain reaction
RAPD	random amplification of polymorphic DNA
RBC	red blood cell
RCT	randomized controlled trial
REA	restriction endonuclease analysis
rep-PCR	repetitive element polymerase chain reaction
RFLP	restriction fragment length polymorphism
RIDDOR	Reporting of Injuries, Diseases and Dangerous Occurrences Regulations
RMAT	rapid micro-agglutination test
RMSF	Rocky Mountain spotted fever
RNA	ribonucleic acid
RPR	rapid plasma reagin
rRNA	ribosomal ribonucleic acid
RSSE	Russian spring–summer encephalitis
RSV	respiratory syncytial virus
RT	reverse transcriptase
RT-PCR	reverse transcription polymerase chain reaction
RVF	Rift Valley fever
s	second
SaBTO	(Advisory Committee on the) Safety of Blood, Tissues and Organs
SaO_2	arterial oxygen saturation
SARS	severe acute respiratory syndrome
SBP	spontaneous bacterial peritonitis
s/c	subcutaneous
SCC	staphylococcal cassette chromosome
SCID	severe combined immunodeficiency disease
sCJD	sporadic Creutzfeldt–Jakob disease
SDD	selective decontamination of the digestive tract
SE	staphylococcal enterotoxin
SENIC	Study on Efficacy of Nosocomial Infection Control
SHOT	Serious Hazards of Transfusion
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIGN	Scottish Intercollegiate Guidelines Network
SIRS	systemic inflammatory response syndrome

SIV	simian immunodeficiency virus
SLE	systemic lupus erythematosus
SLST	single locus sequence typing
S-MAC	sorbitol MacConkey
SMI	Standards for Microbiology Investigations
SNP	single nucleotide polymorphism
slpAST	surface layer protein A gene sequence typing
SOP	standard operating procedure
spp.	species
SPA	suprapubic aspirate
SPS	sodium polyanetholesulphonate
SRSV	small round structured virus
SSA	streptococcal superantigen
SSI	surgical site infection
SSPE	subacute sclerosing panencephalitis
ssRNA	single-stranded ribonucleic acid
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded skin syndrome
STD	sexually transmitted disease
STI	sexually transmitted infection
Stx	shiga toxin
SVR	sustained virological response
SVT	supraventricular tachycardia
TAC	transient aplastic crisis
TB	tuberculosis
TCBS	thiosulfate citrate bile salts sucrose
TCT	tracheal cytotoxin
Td	combined tetanus/low-dose diphtheria vaccine
tds	three times a day
TFT	thyroid function test
TINU	tubulointerstitial nephritis and uveitis
TK	thymidine kinase
TMA	transcription-mediated amplification
TNF	tumour necrosis factor
TOC	test of cure
TOE	transoesophageal echocardiography
TOP	topically

TP	tube precipitin
TPHA	*Treponema pallidum* haemagglutination assay
TPN	total parenteral nutrition
TPPA	*Treponema pallidum* particle assay
TQM	total quality management
TREM-1	triggering receptor expressed on myeloid cells-1
tRNA	transfer ribonucleic acid
TSE	transmissible spongiform encephalopathy
TSS	toxic shock syndrome
TSST	toxic shock syndrome toxin
TST	tuberculin skin test
TTE	transthoracic echocardiography
U&E	urea and electrolyte
UCD	unicentric Castleman's disease
UCV	ultraclean ventilation
UICP	universal infection control precautions
UK	United Kingdom
UKAP	UK Advisory Panel for health-care workers infected with blood-borne viruses
ULN	upper limit of normal
URTI	upper respiratory tract infection
US/USA	United States
USS	ultrasound scan
UTI	urinary tract infection
UV	ultraviolet
VA	ventriculo-atrial
VAP	ventilator-associated pneumonia
VATS	video-assisted thoracoscopic surgery
VCA	viral capsid antigen
vCJD	variant Creutzfeldt–Jakob disease
VDRL	Venereal Disease Research Laboratory (test)
VEE	Venezuelan equine encephalitis
VGK	Vogt–Koyanagi–Harada
VHF	viral haemorrhagic fever
VIP	visual infusion phlebitis (score)
VISA	vancomycin-intermediate *Staphylococcus aureus*
VLM	visceral larva migrans

VNTR	variable-number tandem repeat
VP	ventriculoperitoneal
VRE	vancomycin-resistant enterococci
VRSA	vancomycin-resistant *Staphylococcus aureus*
VSD	ventricular septal defect
VUR	vesico-ureteric reflux
v/v	volume by volume
VZIG	varicella-zoster immune globulin
VZV	varicella-zoster virus
WCC	white cell count
WGS	whole-genome sequencing
WHO	World Health Organization
XDR	extensively drug resistant
XLD	xylose lysine deoxycholate
ZN	Ziehl–Neelsen (stain)

Part 1

Antimicrobials

Chapter 1

Basics of antimicrobials

A history of antibiotics

To start, some definitions: an 'antimicrobial' is an umbrella term for drugs with activity against microorganisms (antibacterials, antivirals, antifungals, antiparasitic agents); an 'antibiotic' is, strictly speaking, a chemical compound made by a microorganism that inhibits or kills other microorganisms at low concentrations. This does not include synthetic agents, although, in practice, it is often used for any antibacterial; an 'antiparasitic' is used to treat parasitic diseases and includes antiprotozoals and antihelminthics.

A history

Substances with some form of anti-infective action have been used since ancient times. The Chinese used 'mouldy' soybean curd to treat boils and carbuncles. The South American Indians chewed cinchona tree bark (contains quinine) for malaria.

In Europe, one of the earliest recorded examples was the use of mercury to treat syphilis in the 1400s.

In 1877, Louis Pasteur showed that injections of extracts of soil bacteria cured anthrax in animals.

In 1908–1910, Paul Erlich, Nobel Prize winner and father of chemotherapy, synthesized arsenic compounds effective against syphilis.

In 1924, the compound actinomycetin, so named because it is produced by actinomycetes, was discovered.

In 1932, Domagk discovered the dye prontosil that cured streptococcal infections in animals. The active group turned out to be the sulfonamide attached to the dye, and, by 1945, over 5000 sulfonamide derivatives had been developed. Adverse effects and drug resistance have limited clinical use of these compounds.

In 1939, Dubos isolated two agents that were active against Gram-positive organisms (gramicidin and tyrocidin) from *Bacillus brevis*.

In 1944–1945, Waksman isolated streptomycin from the soil microbe *Streptomyces griseus*. It was active against *Mycobacterium tuberculosis* and some Gram-negative organisms, and Waksman was awarded the Nobel Prize.

History of penicillin

(See Table 1.1.) Alexander Fleming returned to St Mary's Hospital after a weekend away in 1928 to discover that the mould *Penicillium notatum* had contaminated his culture plates. He observed that the colonies of *Staphylococcus aureus* nearest to the mould had lysed, while those further away had not, and hypothesized that the *Penicillium* had released a product that caused bacterial cell lysis. He called this product penicillin. Although Fleming discovered penicillin, he was unable to purify sufficient quantities for clinical trials. In 1939, Howard Florey, Ernst Chain, and Norman Heatley, working in Oxford, obtained the *Penicillium* fungus from Fleming. They overcame the technical difficulties and conducted clinical trials to demonstrate the efficacy of penicillin. Mass production soon began in the United Kingdom (UK) and United States (USA). Initially, penicillin was used almost exclusively for soldiers injured during the Second World War. It became

widely available by 1946. As soon as he discovered penicillin, Fleming warned of the development of penicillin resistance, and indeed resistance was seen almost immediately. Chemical modifications of the drug have since created derivatives (e.g. ampicillin) that are less susceptible to enzymatic degradation.

Table 1.1 A non-exhaustive antibiotic timeline

Year	Antibiotic	Class of antibiotic
1928	Penicillin discovered	β-lactam
1932	Prontosil discovered	Sulfonamide
1942	Penicillin introduced	β-lactam
1943	Streptomycin discovered	Aminoglycoside
1945	Cephalosporins discovered	β-lactam
1947	Chloramphenicol discovered	Protein synthesis inhibitor
1947	Chlortetracycline discovered	Tetracycline
1949	Neomycin discovered	Aminoglycoside
1952	Erythromycin discovered	Macrolide
1956	Vancomycin discovered	Glycopeptide
1960	Flucloxacillin introduced	β-lactam
1961	Ampicillin introduced	β-lactam
1963	Gentamicin discovered	Aminoglycoside
1964	Cephalosporins introduced	β-lactam
1964	Vancomycin introduced	Glycopeptide
1966	Doxycycline introduced	Tetracycline
1971	Rifampicin introduced	Rifamycin
1974	Co-trimoxazole introduced	Sulfonamide and trimethoprim
1976	Amikacin introduced	Aminoglycoside
1979	Ampicillin/clavulanate introduced	β-lactam/β-lactamase inhibitor
1987	Imipenem/cilastin introduced	Carbapenem
1987	Ciprofloxacin introduced	Quinolone
1993	Azithromycin and clarithromycin introduced	Macrolide
1999	Quinupristin/dalfopristin introduced	Streptogramin
2000	Linezolid introduced	Oxazolidinone
2003	Daptomycin introduced	Lipopeptide
2004	Telithromycin introduced	Ketolide
2005	Tigecycline introduced	Glycylcycline
2012	Fidaxomicin introduced	Macrocyclic

Global antibiotic use

National data on the quantity and trends of antibiotic usage are usually not available. However, it is generally thought that about 50% of all antimicrobials are used in human medicine, and about 50% for animals and crops. The total amount of antimicrobials used varies between countries; developed countries use proportionately more than developing countries. Different countries have different antibiotics available—just because an antibiotic is widely prescribed in one country, it does not mean it will be licensed in another, e.g. teicoplanin is not available in the USA.

Human use of antibiotics

Most infections are treated in the community by general practitioners (GPs) or through outpatient clinics; this accounts for the greatest number of antibiotic prescriptions. Some agents with antimicrobial activity are available over the counter (e.g. clotrimazole for vaginal thrush and topical aciclovir for cold sores). The quantity of antibiotics used varies between hospitals, depending on the specialist units there (e.g. hospitals with large intensive care units (ICUs) or a renal unit are likely to use more antibiotics). Hospitals with similar patient populations have different approaches to prescribing antibiotics, which may be influenced by local antimicrobial susceptibility data. In the first instance, you should follow your local hospital policy and consult microbiology/infectious diseases (ID) specialists for advice.

Problems with human use of antibiotics

Overuse of antibiotics has led to rising rates of resistance to antimicrobials, with the result that a few organisms have become virtually untreatable (e.g. vancomycin-resistant *S. aureus*, extensively drug-resistant (XDR) *M. tuberculosis* (MTB), carbapenemase-producing *Enterobacteriaceae*).

Resistance results in increased morbidity and mortality, with considerable economic and social consequences. In the USA, the Centers for Disease Control and Prevention (CDC) estimates that one-third of all outpatient antibiotic prescriptions is not required. Hence, many organizations have been working to try to reduce inappropriate prescribing, e.g. public education (e.g. most upper respiratory tract infections (URTIs) are caused by viruses), changing the practice of health-care prescribers (e.g. short course, narrow-spectrum agents where appropriate).

Other problems associated with the overuse of antibiotics include superinfection (e.g. with *Candida albicans, Clostridium difficile*), the unnecessary risk of adverse effects, drug interactions, and expense.

In the developing world, a number of additional problems exist:

- antibiotics are often available without prescription from a cornershop;
- if the patient does take an appropriate antibiotic, they may take the wrong dose for the incorrect duration;
- the purchased drug may be inappropriate, so the infection remains untreated, and patients may therefore develop a more severe or complicated infection before consulting a doctor;
- some drugs are 'fake', substandard, or past their expiry date;
- patients may take a combination of traditional therapy along with antibiotics that may lead to interactions and toxicity.

Non-human use of antibiotics

Antimicrobials have been used increasingly for the prevention and treatment of infections in animals (e.g. on farms, in fish factories, and for domestic pets) and in the environment (e.g. crop production). Since the discovery of their growth-promoting abilities, they have also been added to animal feed (particularly for pigs and poultry). In addition, some antibiotics increase feed efficiency (the amount of feed absorbed by an animal), increasing the chance that the animal reaches its target weight on time. Other examples of non-human use include:

- tetracycline sprayed on apple plantations to treat fireblight;
- oxytetracycline added to water in commercial fish farms to treat infections;
- antibiotics used to eliminate bacterial growth inside oil pipelines.

When farm animals consume antibiotics in their feed, they may excrete them into the environment. This may select for antibiotic-resistant organisms that may then infect other animal species. Antibiotics in the environment undoubtedly contribute to increasing antibiotic resistance, particularly amongst food-borne pathogens such as *Salmonella* species (spp.) and *Campylobacter* spp. Many organizations have developed strategies to try to control the non-human use of antibiotics (particularly in agriculture and animal husbandry) and thus reduce the development of resistance.

Responses to the problem of resistance

There is an increasing political awareness of the risk antibiotic resistance poses to human health. Travel and health tourism make it a global issue, from which no one country can isolate itself. England's chief medical officer described it as a 'catastrophic threat', and British and US premiers have backed national plans for research and control. The World Health Organization (WHO) recently conducted a worldwide 'country situation analysis' and is coordinating national responses. Table 1.2 gives sources of information on antimicrobial resistance.

Table 1.2 Sources of information on antimicrobial resistance

Information	Web address
Alliance for the Prudent Use of Antibiotics	www.tufts.edu/med/apua
World Health Organization Drug Resistance	www.who.int/drugresistance/en/
Antibiotic Action	www.Antibiotic-action.com
UK government bodies	www.gov.uk/defra www.gov.uk/phe www.hps.scot.nhs.uk/haiic/amr/
European data (Eurosurveillance)	www.eurosurveillance.org/
National Antimicrobial Resistance Monitoring System (USA)	www.cdc.gov/narms/
British Society for Antimicrobial Chemotherapy	www.bsac.org.uk

Mechanisms of action

Antimicrobial agents are classified by their specific modes of action against bacterial cells. The modes of action of antimicrobial agents against Gram-positive and Gram-negative bacteria are very similar and can be divided into five categories:

- inhibition of cell wall synthesis;
- inhibition of protein synthesis;
- inhibition of nucleic acid synthesis;
- inhibition of folate synthesis;
- disruption of the cytoplasmic membrane.

Inhibition of cell wall synthesis

Agents that interfere with cell wall synthesis block peptidoglycan synthesis or cross-linking. They are active against growing bacteria and are bactericidal.

Gram-negative bacteria—β-lactam antimicrobials enter the cell through porin channels in the outer membrane and bind to penicillin-binding proteins (PBPs) on the surface of the cytoplasmic membrane. This blocks their function, causing weakened or defective cell walls, and leads to cell lysis and death.

Gram-positive bacteria lack an outer membrane, so β-lactam antimicrobials diffuse directly through the cell wall and bind to PBPs, which results in weakened cell walls and cell lysis. Glycopeptides inhibit cell wall synthesis by binding to the D-ALA-D-ALA terminal end of peptidoglycan precursors, thus inhibiting the action of transglycosidase and transpeptidases.

Inhibition of protein synthesis

Tetracyclines bind to the 30S ribosomal subunit, and block attachment of transfer RNA (tRNA) and addition of amino acids to the protein chain. Tetracyclines are bacteriostatic.

Aminoglycosides also bind to the 30S ribosomal subunit and prevent its attachment to messenger RNA (mRNA). They can also cause misreading of the mRNA, resulting in insertion of the wrong amino acid or interference in the ability of amino acids to connect with each other. The combined effect of these two mechanisms is bactericidal.

Macrolides and lincosamides attach to the 50S ribosomal subunit, causing termination of the growing protein chain. They are bacteriostatic.

Chloramphenicol also binds to the 50S ribosomal subunit and interferes with binding of amino acids to the growing chain. It is also bacteriostatic.

Linezolid (an oxazolidinone) binds to the 23S ribosomal RNA (rRNA) of the 50S subunit and prevents formation of a functional 70S initiation complex which is necessary for protein synthesis. It is bacteriostatic.

Inhibition of nucleic acid synthesis

Fluoroquinolones interfere with DNA synthesis by blocking the enzyme DNA gyrase. This enzyme binds to DNA and introduces double-stranded breaks that allow the DNA complex to unwind. Fluoroquinolones bind to the DNA gyrase–DNA complex and allow broken DNA strands to be released into the cell, resulting in cell death.

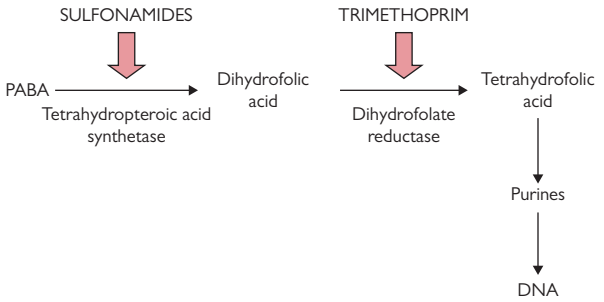

Fig. 1.1 Inhibition of folate synthesis.

Rifampicin binds to DNA-dependent RNA polymerase, which blocks synthesis of RNA and results in cell death.

Inhibition of folate synthesis

(See Fig. 1.1.)

For many organisms, para-aminobenzoic acid (PABA) is an essential metabolite which is involved in the synthesis of folic acid, an important precursor to the synthesis of nucleic acids.

Sulfonamides are structural analogues of PABA and compete with PABA for the enzyme dihydropteroate synthetase.

Trimethoprim acts on the folic acid synthesis pathway at a point after the sulfonamides, inhibiting the enzyme dihydrofolate reductase.

Both trimethoprim and sulfonamides are bacteriostatic. When they are used together (e.g. co-trimoxazole), they produce a sequential blockade of the folic acid synthesis pathway and have a synergistic effect.

Disruption of the cytoplasmic membrane

Polymyxin molecules diffuse through the outer membrane and cell wall of susceptible cells to the cytoplasmic membrane. They bind to the cytoplasmic membrane, and disrupt and destabilize it. This causes the cytoplasm to leak out of the cell, resulting in cell death.

Mechanisms of resistance

There are a number of ways by which microorganisms become resistant to antimicrobial agents. These include:

- production of enzymes;
- alteration in outer membrane permeability;
- alteration of target sites;
- efflux pumps;
- alteration of metabolic pathways.

Production of enzymes

β-lactamases are enzymes that hydrolyse β-lactam drugs. In Gram-negative bacteria, the β-lactam drug enters the cell through the porin channels and encounters β-lactamases in the periplasmic space. This results in hydrolysis of the β-lactam molecules, before they reach their PBP targets. In Gram-positive bacteria, the β-lactamases are secreted extracellularly into the surrounding medium and destroy the β-lactam molecules before they enter the cell.

Aminoglycoside-modifying enzymes—Gram-negative bacteria may produce adenylating, phosphorylating, or acetylating enzymes that modify an aminoglycoside, so that it is no longer active.

Chloramphenicol acetyl transferase—Gram-negative bacteria may produce an acetyl transferase that modifies chloramphenicol, so that it is no longer active.

Alteration in outer membrane permeability

Gram-negative bacteria may become resistant to β-lactam antibiotics by developing permeability barriers.

Mutations resulting in the loss of porin channels in the outer membrane no longer allow the entrance and passage of antibiotic molecules into the cell.

Alterations in proton motive force may result in reduced inner membrane permeability.

Alteration of target sites

PBPs in Gram-positive and Gram-negative bacteria may be altered through mutations, so that β-lactams can no longer bind to them.

Methylation of rRNA confers resistance to macrolides, lincosamides, and streptogramins

Mutations in the chromosomal genes for DNA gyrase and topoisomerase IV confer quinolone resistance.

Efflux pumps

A wide variety of efflux pumps produce antimicrobial resistance in both Gram-positive and Gram-negative bacteria. Transmembrane proteins form channels that actively export an antimicrobial agent out of the cell as fast as it enters. This is the main mechanism of resistance to tetracyclines.

Alteration of metabolic pathways

Some microorganisms develop an altered metabolic pathway that bypasses the reaction inhibited by the antimicrobial. Mutations that inactivate thymidylate synthetase block the conversion of deoxyuridylate to thymidylate. These mutants use exogenous thymine or thymidine for DNA synthesis and therefore are resistant to folate synthesis antagonists.

Molecular genetics of resistance

Genetic variability is essential for microbial evolution and may occur by a variety of mechanisms:

- point mutations;
- rearrangements of large segments of DNA from one location of a bacterial chromosome or plasmid to another;
- acquisition of foreign DNA from other bacteria, via a mobile genetic element (MGE).

Acquisition of resistance, in the presence of the antibiotic, confers a survival advantage on the host, thus leading to the emergence of resistant clones. The overuse, incorrect use, or injudicious use of antibiotics contributes to this problem, and explains why new resistance patterns tend to emerge in areas of the hospital with the greatest antibiotic consumption (e.g. ICUs). This antibiotic resistance may be passed vertically to future generations through clonal expansion, resulting in a bacterial population that is resistant to an antibiotic.

Point mutations

These are often referred to as single nucleotide polymorphisms (SNPs). The bacterial genome is dynamic, in that bacteria are constantly undergoing mutations. Some of these mutations will (by chance) result in a survival advantage to the organism, e.g. due to increased virulence or antibiotic resistance. In certain environments, these will be preferentially selected for; thus, the mutation that arose by chance will be retained and passed to future generations. Examples of point mutations include the generation of β-lactamase and fluoroquinolone resistance.

Mobile genetic elements

These are pieces of DNA that can move around between genomes. They may thus be involved in the horizontal transfer of resistance genes between bacteria, as opposed to the vertical transfer of resistance by clonal expansion (see list below). Bacterial genomes consist of core genes and accessory genes; it is the latter that are defined by acquisition and loss. There are several different MGEs described in the following list.

- Plasmids—these are extrachromosomal pieces of circular DNA, which vary in size from 10kb to over 400kb. In addition to carrying resistance genes, they may determine other functions, e.g. virulence factors and metabolic capabilities. They are autonomous self-replicating genetic elements that possess an origin for replication and genes that facilitate their maintenance in the host bacteria. Conjugative plasmids require additional genes to initiate self-transfer.
- Insertion sequences (IS)—these are short DNA sequences that are usually only 700–2500bp (base pairs) long. They encode an enzyme needed for transposition (i.e. to excise a segment of DNA from one position in the chromosome and insert it elsewhere) and a regulatory protein, which either stimulates or inhibits the transposition activity. They are thus different from transposons, which also carry accessory

genes such as antibiotic resistance genes. The coding region in an insertion sequence is usually flanked by inverted repeats.

- Transposons—these are often called 'jumping genes' and may contain IS. They cannot replicate independently but can move between one replicating piece of DNA to another, e.g. from a chromosome to a plasmid. Conjugative transposons mediate their own transfer between bacteria, whereas non-conjugative transposons need prior integration into a plasmid to be transferred.
- Integrons—these may be defined as a genetic element that possesses a site (*attI*) at which additional DNA in the form of gene cassettes can be integrated by site-specific mutation. They also encode a gene, integrase, which mediates these site-specific recombination events. Gene cassettes normally consist of an antibiotic resistance gene and a 59-base element that functions as a site-specific recombination site. The largest integrons (e.g. in *Vibrio cholerae*) can contain hundreds of gene cassettes.
- Bacteriophages—a bacteriophage is a virus that infects bacteria and may become integrated into the bacterial chromosome (and is then called a prophage). They typically consist of an outer protein enclosing genetic material (which may be single- or double-stranded DNA or RNA). Bacteriophages may be considered MGEs but are rarely involved in the transfer of resistance genes. They have been used as an alternative to antibiotics (phage therapy) in Eastern Europe and the former USSR for ~60 years.

Clonal expansion

Clonal expansion refers to the multiplication of a single 'ancestor' cell. This may result in the propagation of antibiotic resistance into daughter cells. The antibiotic resistance genes will be passed from one generation of bacteria to the next, which is also called vertical transfer of resistance. If an organism becomes resistant to an antibiotic, either by mutation or acquisition of an MGE, it will have a survival advantage in an environment where that antibiotic is present. Thus, the daughter cells that are generated will be positively selected for, over daughter cells from another antibiotic-sensitive strain of the bacteria, and future generations will be resistant to that agent. A bacterial clone refers to all organisms that are likely to have arisen from a common ancestor. This may not be immediately obvious. Examples of recent clonal expansion relating to the spread of antibiotic resistance genes are meticillin-resistant *S. aureus* (MRSA) and penicillin-resistant pneumococci.

Important definitions

Isolate: this refers to a pure culture. It says nothing about typing.

Clone: this refers to bacterial cultures which have been isolated independently, from different sources, in different places, and maybe at different times, but are so similar phenotypically and genotypically that the most likely explanation is that they arose from a common ancestor.

Strain: this refers to a phenotypically and/or genotypically distinctive group of isolates. It is dependent on the typing scheme used, and some experts suggest avoiding the use of this term.

Type: this refers to organisms with the same pattern or set of markers displayed by a strain, when the bacteria are subject to a particular typing system.

Heteroresistance

This is defined as the growth of one bacterial subpopulation at a higher antibiotic concentration than predicted by the minimum inhibitory concentration (MIC) for most cells. Heteroresistance may be difficult to diagnose and result in poor response to treatment. Examples include:

- *S. aureus* and vancomycin;
- *Cryptococcus neoformans* and azoles;
- MTB and rifampicin;
- *Enterococcus faecium* and vancomycin;
- *Acinetobacter baumanii* and carbapenems and colistimethate sodium;
- *Helicobacter pylori* and metronidazole and amoxicillin;
- *Streptococcus pneumoniae* and penicillin.

Susceptibility testing

Bacteriostatic

Antibiotics that inhibit growth and replication of bacteria, but are non-lethal (e.g. drugs that inhibit folic acid synthesis; ➔ see Trimethoprim, pp. 60–1; ➔ Co-trimoxazole, pp. 61–2; ➔ Quinolones, pp. 62–4).

Bactericidal

Antibiotics that cause bacterial cell death by inhibition of: (a) cell wall synthesis, (b) nucleic acid synthesis, or (c) protein synthesis. Some antibiotics may be bacteriostatic at low concentrations, but bactericidal at higher concentrations.

Minimum inhibitory concentration

This is the concentration of antimicrobial required to completely inhibit the growth of an organism after a defined time period (usually overnight). It is determined by agar dilution (incubation on multiple plates with differing antibiotic concentrations) or broth microdilution (liquid broth with varying concentrations of antibiotic—a technique used by many automated systems). Performing MIC testing on a number of strains of a single species allows estimation of the concentration that will inhibit 90% (MIC_{90}) or 50% (MIC_{50}) of that isolate *in vitro* and can detect shifts in antibiotic susceptibility in bacterial populations.

Minimum bactericidal concentration

This is the concentration of antimicrobial required to kill a bacterium. It can be determined from broth dilution tests by subculturing the overnight culture to agar containing no antibiotic. Minimum bactericidal concentration (MBC) is considered the lowest concentration capable of reducing the original inoculum by a factor of 1000 (e.g. from 10^5 cfu/mL to 10^2 or less).

Susceptibility testing techniques

Dilution methods—agar and broth dilution (➔ see Minimum inhibitory concentration, p. 13). The former is considered the gold standard due to good reproducibility. Both are labour-intensive, if performed manually. They should be performed, following the standardized guidelines of a reference body such as the British Society for Antimicrobial Chemotherapy (BSAC), the European Committee on Antimicrobial Susceptibility Testing (EUCAST), or the Clinical & Laboratory Standards Institute (CLSI).

Disc diffusion—efficient and cost-effective, and the most widely used manual method. There are a number of standard methods for performing disc diffusion (Kirby–Bauer, Stokes), and, as a number of factors can influence performance (e.g. agar depth, time, temperature), it is important they are followed. In essence, an agar preparation is evenly seeded with the organism of interest. Commercially prepared discs, each impregnated with a standard concentration of a relevant antibiotic, are placed on the agar surface. The antibiotic diffuses into the agar. After overnight incubation, the bacterial growth around each disc is observed. The zone around the disc with no growth ('zone of inhibition') contains sufficient agent to prevent growth. This zone is measured and compared to the published 'zone breakpoint diameter' for that particular organism/antibiotic combination. It is a qualitative test, and the MIC cannot be derived, but the organism is classed as susceptible, intermediate, or resistant.

E-test—a commercial product taking the form of a plastic strip impregnated with a steadily decreasing concentration of a single antibiotic. It is placed on an agar plate already seeded with the organism of interest. The MIC can then be read from the strip at the point at which bacterial growth is inhibited.

Automated systems—a number of commercial systems now exist that provide standard microdilution plates preloaded with antibiotics (and biochemical assays relevant to organism identification). They are costly to purchase and maintain, but they reduce technical errors and lengthy preparation time.

Mechanism-specific tests—certain phenotypic tests may enable inference of the presence of a resistance mechanism. For example, chromogenic systems for detection of MRSA or cephalosporinase.

Genotypic methods—specific genes encoding resistance mechanisms can be detected by techniques such as polymerase chain reaction (PCR) and DNA hybridization. However, the presence of a gene may not equate to treatment failure (its product may be expressed only at a low level), and its absence clearly does not exclude the presence of another means of resisting a particular agent.

Sensitive or resistant?

A 'breakpoint' is the antibiotic concentration used in the interpretation of susceptibility testing to define isolates as susceptible, intermediate, or resistant. This is not the same as the MIC and may take into account *in vitro* potency, pharmacokinetics/dynamics, clinical experience, and infection site. Increasingly, national authorities think in terms of 'clinical' breakpoints to guide prescribers for specific patients and 'microbiological' breakpoints which seek to identify strains that do not belong to the normal antibiotic-naïve population for the purposes of surveillance.

In January 2016, the BSAC ceased support and development of the BSAC disc diffusion method as part of a national move to the EUCAST disc diffusion method. The EUCAST method is based on the Kirby–Bauer method and uses Mueller–Hinton agar. Full details on the EUCAST method and breakpoint setting are available at www.eucast.org/clinical_breakpoints/.

Pharmacokinetics

This is what the body does to the drug; it comprises absorption, distribution, metabolism, and excretion (mnemonic ADME).

Absorption

To be effective, a drug must reach the site of the infection. In some cases, this is possible by topical application (e.g. nystatin pastilles for oral candidiasis), but, in most cases, drugs are transported around the body by the circulation.

Some drugs are poorly absorbed when given by mouth (e.g. aminoglycosides and glycopeptides) and are therefore given parenterally. Occasionally, oral drugs may be used to treat luminal infections, e.g. vancomycin for *C. difficile*.

If a drug is absorbed when given by mouth, the proportion that is absorbed into the systemic circulation is called the bioavailability. Drugs given intravenously (IV) have 100% bioavailability. The time profile of absorption versus elimination is usually more important than the total amount of drug absorbed (see Pharmacodynamics, pp. 16–8).

Absorption may be affected by interactions with other drugs or food that may bind the drug (e.g. tetracyclines should not be given with milk). Altered physiology (e.g. diarrhoea) may reduce absorption. None of the commonly prescribed antibiotics are subject to significant first-pass metabolism in the liver.

Distribution

The volume of distribution relates the drug concentration in the blood to the amount of drug given. A drug with a small volume of distribution is largely confined to the plasma. A drug with a large volume of distribution is widely distributed, e.g. fat-soluble drugs.

Box 1.1 Antimicrobials metabolized by CYP3A4

- Inducers—rifampicin.
- Inhibitors—ketoconazole, itraconazole, erythromycin, clarithromycin.
- Substrates—ritonavir, saquinavir, indinavir, nelfinavir.

Metabolism

Some antibiotics are metabolized in the liver by isoforms of cytochrome P450, of which the CYP3A4 isoform is the most abundant (see Box 1.1). Rifampicin induces the activity of CYP3A4, leading to increased metabolism (and reduced efficacy) of drugs that share this pathway, e.g. human immunodeficiency virus (HIV) protease inhibitors (PIs). In contrast, the azole antifungals and the macrolides inhibit the activity of CYP3A4, which will reduce the metabolism (and may increase toxicity) of drugs also metabolized by this isoform. Always check for interactions before starting or stopping antibiotics, and seek expert advice if unsure.

Excretion

This can be divided into renal (e.g. aminoglycosides, glycopeptides) and non-renal (biliary tree, e.g. ceftriaxone; gastrointestinal (GI) tract, e.g. azithromycin). Clearance determines the half-life of the drug (the time for the blood concentration to decrease by half). Steady state generally occurs when a patient has taken the drug for a period of time equal to 5–7 half-lives. Calculating the creatinine clearance (CrCl) (➔ see Antimicrobials in renal impairment, pp. 21–3) as a measure of renal function can be essential for safe dosing of some renally excreted drugs, such as once-daily aminoglycosides (➔ see Aminoglycosides, pp. 46–8).

Pharmacodynamics

The study of the biochemical and physiological effects of a drug on the body or microorganism, and the mechanism of drug action, including the link between concentration and effect.

Effects on the body

These may be desired (the therapeutic action of the agent) or undesirable (side effects, e.g. diarrhoea, neuropathy, ototoxicity, etc.). The balance between them is influenced by the therapeutic window—the difference between the dose that is effective (desired) and the dose that gives more adverse undesired effects than desired. Drugs with narrow windows may require therapeutic drug monitoring (e.g. gentamicin).

Synergism

This occurs when the activity of two drugs together is greater than the sum of their actions if each were given separately. An example is the use of ampicillin and gentamicin for enterococcal infections (➔ see Enterococci, pp. 245–7) where ampicillin acts on the cell wall to enable gentamicin to gain entry to the cell and act on the ribosome.

Antagonism

One drug diminishes the activity of another drug, so giving both antibiotics together may result in a worse clinical outcome than just giving one antibiotic. For example, co-administration of a bacteriostatic agent (e.g. tetracycline) with a β-lactam may inhibit cell growth and prevent the bactericidal activity of the β-lactam.

Concentration-dependent killing

The antibiotic kills the organism when its concentration is well above the MIC of the organism. The greater the peak, the greater the killing, e.g. once-daily dosing of gentamicin (➔ see Aminoglycosides, pp. 46–8).

Time-dependent killing

The antibiotic *only* kills the bacteria when its concentration is above the MIC of the organism, but increasing the concentration does not lead to increased killing. If the concentration rises above four times the MIC, any additional effect is negligible. Most recommended dosing schedules account for this (➔ see Penicillins, pp. 32–3; ➔ Cephalosporins, pp. 33–5; ➔ Macrolides, pp. 48–50). On a practical level, it is important when adjusting the dose of glycopeptides (➔ see Glycopeptides, pp. 42–4).

Post-antibiotic effect

The post-antibiotic effect (PAE) is defined as the time during which bacterial growth is inhibited after antibiotic concentrations have fallen below the MIC. The mechanism is unclear, but it may be due to a delay in the bacteria re-entering a log-growth period. Several factors influence the presence or duration of the PAE, including the type of organism, type of antimicrobial, concentration of antimicrobial, duration of antimicrobial exposure, and antimicrobial combinations. *In vitro*, β-lactam antimicrobials demonstrate a PAE against Gram-positive cocci, but not against Gram-negative bacilli. Antimicrobials that inhibit RNA or protein synthesis produce a PAE against Gram-positive cocci and Gram-negative bacilli. The clinical relevance of the PAE is probably most important when designing dosage regimens. The presence of a long PAE allows aminoglycosides to be dosed infrequently; the lack of an *in vivo* PAE suggests that β-lactam antimicrobials require frequent or continuous dosing.

Eagle effect

This is a paradoxical effect, first described by Eagle in 1948, whereby higher concentrations of penicillin resulted in decreased killing of staphylococci and streptococci. Eagle also showed that this paradoxical effect seen *in vitro* correlated with an adverse outcome *in vivo*. This effect has since been described with a number of other antimicrobials and organisms, e.g. ampicillin and *Enterococcus faecalis*, carbenacillin and *Proteus mirabilis*, mecillinam and *Providencia stuartii*, cefotaxime and *S. aureus* and *Pseudomonas aeruginosa*, and aminoglycosides and Gram-negative bacteria.

Preventing the development of resistance

Studies are focusing on defining the breakpoints that predict the emergence of resistance. An ideal antibiotic should have a low rate of resistance

mutation, high-fitness cost of resistance, and low rate of fitness-restoring complementary mutation. Novel parameters that are being investigated include:

- mutant prevention concentration—the ability to restrict the selection of resistant mutants;
- mutant selection window—the concentration range between the minimal concentration required to block the growth of wild-type bacteria, up to the concentration needed to inhibit the growth of the least susceptible single-step mutant. There are different concentration ranges for each organism/drug combination.

Routes of administration

Oral administration

Most antibiotics used in human medicine are given orally (PO) in the community. If a drug is absorbed when given by mouth, the proportion that is absorbed into the systemic circulation is called the bioavailability (➔ see Pharmacokinetics, pp. 15–6). This depends on the formulation of the drug and how it is taken, e.g. some tetracyclines should not be taken with milk or antacids, as these decrease their absorption. Some drugs are not absorbed when given PO. This can be advantageous when treating luminal infections, e.g. oral vancomycin for *C. difficile* and neomycin in hepatic failure.

Intravenous administration

The IV route enables higher doses to be given and results in higher, more reliable drug concentrations (see Box 1.2).

Indications

Antimicrobials are given IV in the following situations:

- life-threatening infections, e.g. meningitis, septicaemia, endocarditis, require IV therapy. Antibiotics may be given as infusions or bolus doses, depending on the drug;
- inability to take/absorb oral medications, e.g. nil by mouth, severe vomiting or diarrhoea, oesophageal or intestinal obstruction, post-operative ileus;
- poor oral bioavailability—some drugs are not absorbed if given PO, e.g. aminoglycosides, glycopeptides, colistimethate sodium.

Box 1.2 Practical points

- Many people believe that IV antibiotics are somehow 'stronger' than oral antibiotics. This is not necessarily the case (e.g. ciprofloxacin is as effective when given PO as when given IV and much cheaper).
- The oral and IV doses of the same antibiotic may be different (e.g. metronidazole).

Disadvantages

IV therapy may be associated with a number of problems:

- side effects, which may be local (e.g. phlebitis) or systemic (e.g. rapid infusion may result in anaphylactoid reactions such as the 'red man syndrome' with vancomycin);
- line infections, which may be local (e.g. exit site, tunnel or pocket infections) or systemic (e.g. bacteraemia, endocarditis);
- inconvenience to the patient;
- need to stay in hospital. This may be overcome by the use of outpatient antimicrobial therapy (OPAT) which is now available in some regions of the UK;
- IV antibiotics are usually considerably more expensive than the oral formulation.

IV to oral switch

As a result of the problems associated with IV therapy, many hospitals employ 'IV to oral switch' protocols for certain conditions which encourage clinicians to change to oral antibiotics as soon as is safe. Criteria include:

- suitable oral agent available;
- the patient can tolerate, swallow, and absorb oral antibiotics;
- no symptoms or signs of ongoing sepsis;
- some conditions are specifically excluded (e.g. meningitis and endocarditis). If in doubt, consult an infection specialist.

Intramuscular administration

This is an infrequent method of administration, largely because absorption is unpredictable and the injection may be painful. Local side effects include irritation and development of a sterile abscess. The advantages are that there is no question of compliance and the agent can be administered easily in the community. Intramuscular (IM) administration is commonly used for vaccinations, in genitourinary (GU) clinics, and for tuberculosis (TB) treatment in the developing world.

Never give IM injections to patients with bleeding/clotting disorders, e.g. thrombocytopenia, haemophilia.

Examples of drugs given intramuscularly

Benzylpenicillin should be given immediately if a GP suspects bacterial meningitis (especially meningococcal disease) in the community, before transferring the patient urgently to hospital. If it cannot be administered IV, then deep IM injection is recommended.

Procaine penicillin (procaine benzylpenicillin) is given as daily IM injections in early syphilis or late latent syphilis. It is only available on a named patient basis.

Cefotaxime IM may be given as secondary prophylaxis for contacts of meningococcal disease, if the individual is unable to take rifampicin or ciprofloxacin (although it is not licensed for this indication).

Ceftriaxone IM is used for gonococcal infection (particularly pharyngeal or conjunctival infection).

Spectinomycin IM is occasionally given to patients who cannot take cephalosporins or quinolones (e.g. pregnant women with β-lactam allergy).

Streptomycin IM is commonly given for the treatment of TB in the developing world.

Gentamicin IM is sometimes given before changing a urinary catheter in a patient in the community.

Topical administration

Many antimicrobials are available as topical (TOP) preparations. They are most commonly used in general practice and dermatology. However, they are not without risk and should be used with caution. Before prescribing a topical drug, consider the following.

- Does the condition require treatment? Not all skin conditions that are oozing, crusted, or pustular are infected. Would improving hygiene resolve the situation? Even if an organism is cultured from a swab, it may represent colonization and not require treatment.
- Would systemic antibiotics be more appropriate? Some skin infections (e.g. erysipelas, cellulitis) require systemic antibiotics, as the infection is too deep for topical antibiotics to penetrate adequately.
- Development of resistance—topical antibacterials should be limited to those not used systemically, in order to prevent the development of resistance.
- Duration of treatment—topical agents should only be used for short periods in defined infections.

Examples of drugs given topically

Fusidic acid may be used to treat impetigo, although oral therapy is often required. It should not be used for >7–10 days.

Mupirocin may also be used to treat impetigo (if MRSA-positive) or given as part of MRSA decolonization regimens. It should not be used for >7–10 days.

Neomycin is also used to treat skin infection but may cause ototoxicity, if large areas of skin are treated, and sensitization.

Chloramphenicol may be given as eye drops or ear drops for conjunctivitis or otitis externa, respectively.

Aciclovir cream may be used for the treatment of oral and genital herpes simplex infections.

Nystatin pastilles can be used for oral candidiasis.

Clotrimazole cream is used for vulvovaginal candidiasis or athlete's foot.

Permethrin and malathion are used for scabies.

Malathion, pyrethroids, or dimeticone may be used for head lice.

Aerosolized administration

Aerosolized antibiotics are usually given for treatment or prophylaxis of respiratory infections. They are administered directly to the site of action and may have fewer systemic adverse effects. However, they are usually more difficult to give, and there may still be some systemic absorption. One of the main groups to benefit from aerosolized antibiotics are cystic fibrosis (CF) patients, who may acquire multiresistant organisms (➔ see Cystic fibrosis, pp. 623–5).

Examples of antimicrobials given by inhalation

Tobramycin (➔ see Aminoglycosides, pp. 46–8) is an aminoglycoside often given by nebulizer for chronic pulmonary infection with *P. aeruginosa* in CF patients. It is usually given cyclically (twice daily for 28 days, followed by a 28-day tobramycin-free period). Not all patients respond to treatment, and some become less responsive as drug resistance develops.

Colistimethate sodium (➔ see Polymyxins, pp. 68–9) is a polymyxin antibiotic active against many Gram-negative organisms, including *P. aeruginosa* and *Acinetobacter* spp. It is not absorbed PO and is toxic when given systemically, so inhalation of a nebulized (neb) solution is the preferred route for treating respiratory infections. It is mainly used as an adjunct to standard antibiotics in CF patients. It has also been used for the prevention and treatment of ventilator-associated pneumonia (VAP) due to *Acinetobacter* spp., although this practice is controversial.

Pentamidine isethionate (➔ see Antiprotozoal drugs, pp. 119–24) is used as a second-line agent for the treatment of *Pneumocystis jiroveci* pneumonia (➔ see *Pneumocystis jiroveci*, pp. 482–4). In mild disease, inhaled pentamidine may be used in patients who are unable to tolerate co-trimoxazole, but systemic absorption may occur. In severe disease, IV pentamidine is used in patients who are unable to tolerate, or have not responded to, co-trimoxazole. Side effects include hypotension following administration, and severe, sometimes fatal, reactions due to hypotension, hypoglycaemia, pancreatitis, and arrhythmias. Intermittent inhaled or IV pentamidine may be used as prophylaxis in patients unable to tolerate co-trimoxazole (although inhaled pentamidine does not protect against extrapulmonary disease).

Ribavirin (➔ see Antivirals for respiratory syncytial virus, p. 96) is licensed for the treatment of severe respiratory syncytial virus (RSV) bronchiolitis in infants and children, especially if they have other serious diseases. There is no evidence of mortality benefit. Side effects include worsening respiration, bacterial pneumonia, and pneumothorax. CAUTION: ribavirin is teratogenic, and exposure should be avoided in pregnant and breastfeeding women.

Antimicrobials in renal impairment

General principles

- Avoid nephrotoxic drugs in patients with renal impairment.
- Keep antibiotic prescriptions to a minimum for patients with severe renal disease.
- Some IV antibiotic preparations contain sodium (e.g. Tazocin®), which may cause difficulties in patients with renal impairment.
- The use of drugs in patients with renal impairment can cause several problems:
  - reduced excretion of a drug or its metabolites may cause toxicity;
  - increased sensitivity to some drugs;

  - many side effects are poorly tolerated in patients with renal impairment;
  - some drugs are not effective when renal function is impaired.
- Some of these problems may be avoided by reducing the dose (or using alternative drugs).

Assessment of renal function

Renal function can be assessed in a number of ways.

- Serum creatinine is the most commonly used parameter. It is affected by muscle mass which may be reduced in elderly patients (resulting in underestimation of renal impairment) or increased in certain races (e.g. blacks). Serum creatinine does not rise until 60% of total kidney function is lost.
- CrCl can be measured using a 24-h urine collection. Estimated CrCl is calculated using the Cockcroft and Gault formula (see Box 1.3), which is based on age, weight, sex, and serum creatinine. Thus, estimated CrCl may be inaccurate in patients who are obese or have acute renal failure.
- Glomerular filtration rate (GFR) is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time, and can be measured by injecting inulin into the plasma. Estimated GFR (eGFR) can be calculated using the modification of diet in renal disease (MDRD) formula (see Box 1.4), which is based on serum creatinine, age, sex, and race. Renal impairment was previously classified into three grades (mild, moderate, and severe); this has now been superseded by the use of CrCl or GFR.

Dose modification in renal impairment

- The level of renal function below which the dose of a drug must be reduced depends on the proportion of the drug eliminated by renal excretion and its toxicity.
- For drugs with only minor or no dose-related side effects, very precise modification of the dose regimen is unnecessary, and a simple scheme for dose reduction is sufficient.
- For more toxic drugs with a small safety margin, dose regimens based on GFR should be used.

Box 1.3 Cockcroft and Gault formula for estimated creatinine clearance

$$[CrCl\ (mL/min) = (140 - age) \times lean\ body\ weight\ (kg) \times N]/ serum\ creatinine\ (micromole/L)$$

NB. N = 1.23 for males and 1.03 for females.

Box 1.4 MDRD formula for estimated glomerular filtration rate

$$eGFR\ (mL/min/1.73m^2) = 186 \times (serum\ creatinine / 88.4)^{-1.154} \times (age)^{-0.203} \times (0.742\ if\ female)\ or \times (1.21\ if\ black)$$

- When both efficacy and toxicity are closely related to plasma drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and plasma drug concentration (e.g. vancomycin, gentamicin).
- The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced, it is important to give a loading dose if an immediate effect is required. The loading dose should usually be the same size as the initial dose for a patient with normal renal function.
- Seek specialist advice from your hospital pharmacist for patients on haemodialysis, haemofiltration, or chronic ambulatory peritoneal dialysis.

Drugs to be used with caution

- For up-to-date guidance, always consult your hospital pharmacist, the *British National Formulary* (*BNF*), or the electronic *Medicines Compendium* (🔗 www.medicines.org.uk/emc/).
- A wide range of antimicrobials should be used with caution in patients with renal impairment, including:
  - antibacterials, e.g. aminoglycosides, aztreonam, cephalosporins, carbapenems, chloramphenicol, colistimethate sodium, ethambutol, isoniazid, linezolid, macrolides, ketolides, penicillins, quinolones, sulfonamides, tetracyclines, trimethoprim, vancomycin;
  - antifungals, e.g. amphotericin, flucytosine, fluconazole, itraconazole, voriconazole;
  - antimalarials, e.g. atovaquone, chloroquine, atovaquone/proguanil, proguanil, pyrimethamine, quinine, artemether with lumefantrine, sulfadiazine;
  - antivirals, e.g. aciclovir, adefovir, amantadine, antiretrovirals, famciclovir, foscarnet, ganciclovir, oseltamivir, pentamidine, ribavirin, valaciclovir, valganciclovir.

Antimicrobials in liver disease

Metabolism by the liver is the main route of elimination for many drugs, but hepatic reserve is large, and liver disease has to be severe before important changes in drug metabolism occur. Routine liver function tests (LFTs) are a poor guide to metabolic capacity, and it is not possible to predict the extent to which the metabolism of a particular drug may be impaired in an individual patient. Drug prescribing should be kept to a minimum in all patients with severe liver disease.

Effect of liver disease on response to drugs

Liver disease may alter the response to drugs in several ways:

- impaired drug metabolism may lead to increased toxicity;
- hypoproteinaemia results in reduced protein binding and increased toxicity of highly protein-bound drugs, e.g. phenytoin;

- reduced synthesis of clotting factors increases the sensitivity to oral anticoagulants;
- hepatic encephalopathy may be precipitated by certain drugs, e.g. sedative drugs, opioid analgesics, diuretics, and drugs that cause constipation;
- fluid overload (ascites, oedema) may be exacerbated by drugs that give rise to fluid retention, e.g. non-steroidals and corticosteroids;
- hepatotoxicity is either dose-related or unpredictable (idiosyncratic), and is more common in patients with liver disease.

Drugs to be used with caution

- For up-to-date guidance, always consult your hospital pharmacist or the *BNF*.
- The following antimicrobials should be used with caution in liver disease:
  - antibacterials, e.g. ceftriaxone, chloramphenicol, co-amoxiclav, co-trimoxazole, daptomycin, flucloxacillin, fusidic acid, isoniazid, macrolides, ketolides, linezolid, meropenem, metronidazole, moxifloxacin, neomycin, ofloxacin, rifamycins, sodium fusidate, quinupristin/dalfopristin, tetracyclines, tigecycline, tinidazole, ticarcillin/clavulanic acid;
  - antifungals, e.g. azoles, caspofungin, griseofulvin, terbinafine;
  - antimalarials, e.g. mefloquine, pyrimethamine, artemether with lumefantrine;
  - antivirals, e.g. antiretrovirals, interferons (IFNs), ribavirin, valaciclovir.

Antimicrobials in pregnancy

Caution should be exercised in prescribing any medication in pregnancy. When it is necessary to use antibiotics, the prescriber should bear in mind the gestational age and balance the risk of teratogenesis or other complication with the risk of failing to treat the mother effectively. Many antibiotic agents have very limited data available on their use in pregnancy. The following advice is general, and prescribers should check a current formulary (e.g. *BNF*) for the latest data on the agent they plan to use.

Specific agents

- Penicillins—considered safe in pregnancy. Trace amounts can be found in breast milk, but most are considered safe to use. Limited data regarding the use of piperacillin with tazobactam (Tazocin®) has led the manufacturer to recommend its use only if benefit outweighs risk.
- Cephalosporins—generally considered safe for use in pregnancy. Some may cross into breast milk at low levels. The manufacturers of cefixime and ceftaroline recommend avoiding use when breastfeeding.
- Carbapenems—manufacturers recommend use only if benefit outweighs the potential risk. All may be found in milk, and, while it is unlikely they would be absorbed, the manufacturer recommends avoiding.
- Tetracyclines—affect skeletal development in the first trimester in animal studies and deposit in growing bones and teeth. Should not be given to pregnant or breastfeeding women. Maternal hepatotoxicity has been reported.

- Aminoglycosides—avoid unless essential (in which case meticulous therapeutic monitoring is required) due to the risk of auditory and vestibular nerve damage. The risk is greatest in the second/third trimesters.
- Macrolides—erythromycin is not known to be harmful in pregnancy, and only small amounts are found in breast milk. The others, including clarithromycin, have more limited data and should only be used if there are no alternatives and benefit outweighs risk.
- Clindamycin—not known to be harmful in pregnancy, and only very small amounts cross into breast milk. Bloody diarrhoea has been reported in one infant.
- Glycopeptides—limited data. Use if benefit outweighs risk, and monitor levels carefully. Present in milk, but significant absorption by infant is unlikely.
- Co-trimoxazole and trimethoprim—avoid folate antagonists with a teratogenic risk in the first trimester. Co-trimoxazole has the additional risks of neonatal haemolysis and methaemoglobinaemia in the third trimester, and a small risk of kernicterus in jaundiced babies and haemolysis in the glucose-6-phosphate dehydrogenase (G6PD)-deficient baby if breastfed.
- Metronidazole—probably safe, but manufacturer recommends avoiding high-dose regimes.
- Quinolones—avoid in pregnancy. Associated with arthropathy in animal studies. Present in small amounts in breast milk. Probably harmless, but manufacturer recommends to avoid.
- Nitrofurantoin—safe to use in pregnancy, but avoid at term due to association with neonatal haemolysis.

Antimicrobial prophylaxis

Definitions

Prophylaxis is the administration of antibiotics to prevent the infection of a previously uninfected tissue. Primary prophylaxis aims to prevent initial infection or disease (e.g. to cover a surgical procedure), while secondary prophylaxis aims to prevent recurrent disease (e.g. giving penicillin to a patient who has had rheumatic fever). Surgical prophylaxis is usually primary and aims to target the operative period when the site may become contaminated.

Principles of antimicrobial prophylaxis

All hospitals should have a policy for prescribing antimicrobial prophylaxis for common procedures, which may be area-/unit-/surgeon-specific. The following factors should be considered.

- Before prescribing, always consider:
  - does the patient have any known drug allergies?
  - has the patient received any recent antibiotics?
  - is the patient known to be colonized with resistant organisms?

- Which drug? A bactericidal agent should be used which:
  - is active against the probable infecting organism(s);
  - penetrates the likely site of infection;
  - has a favourable safety profile.
- What dose? The aim is to maintain the drug concentration above the target MIC throughout the operative period. The number of doses usually depends on the length of procedure and likely blood loss.
- Which route? This depends on the nature of the procedure, whether or not the patient is nil by mouth, and the pharmacokinetics of the drug.
- Time of administration? Antimicrobial prophylaxis should be administered 0–2h prior to the procedure, in order to ensure adequate tissue levels.
- Duration? Prophylactic antibiotics should not usually be given for >24h. If there is evidence of infection, the patient should be carefully assessed, and appropriate cultures sent. The organisms responsible for post-operative infections are unlikely to be sensitive to the prophylactic antibiotics. Seek advice on antimicrobial therapy from an infection specialist in light of the clinical picture and likely infecting organisms.

Risks of antimicrobial prophylaxis

While the benefit of prophylactic antibiotics is clear, there are also potential risks. These include:

- adverse effects associated with specific drug (e.g. penicillin anaphylaxis);
- selection of antibiotic-resistant organisms;
- alteration of normal flora.

Before prescribing antimicrobial prophylaxis for a procedure, consider whether it is actually needed. Consult your local antibiotic policy, or seek advice from an infection specialist if unsure.

Detailed indications for prophylaxis

For up-to-date information, consult the *BNF*. Antimicrobial prophylaxis is currently recommended in the following situations:

- prevention of recurrence of rheumatic fever;
- prevention of a secondary case of group A streptococcal (GAS) infection;
- prevention of a secondary case of meningococcal infection;
- prevention of a secondary case of *Haemophilus influenzae* type b disease;
- prevention of a secondary case of diphtheria in a non-immune contact;
- prevention of a secondary case of pertussis in a non-immune or partially immune contact;
- prevention of pneumococcal infection in asplenia or sickle-cell disease;
- prevention of gas gangrene in high lower-limb amputations or following major trauma;
- prevention of TB in susceptible close contacts or those who become tuberculin skin test (TST)-positive;
- prevention of infection in certain GI procedures;
- prevention of infection in certain obstetric/gynaecological, orthopaedic, urological, and vascular surgery;

- prevention of endocarditis is now only recommended for 'at-risk' patients undergoing a GI or GU procedure where infection is suspected. At-risk groups include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural heart disease (excluding isolated atrial septal defects (ASDs), fully repaired ventricular septal defects (VSDs), fully repaired patent ductus arteriosus (PDA), and endothelialized closure devices), hypertrophic cardiomyopathy, or a previous episodes of endocarditis.

Other examples of antimicrobial prophylaxis

- Selective decontamination of the digestive tract (SDD)—administration of antibiotics that are poorly absorbed when given PO to eliminate normal GI flora. Some ICUs use it to prevent VAP. This practice is controversial.
- Local infiltration into wound/incision line—current data suggest this can lead to higher rates of infection, unless combined with systemic administration. There is no additional reduction in wound infections if antibiotics are given by both routes simultaneously, compared with systemic antibiotics alone.
- Antibiotic-impregnated materials—gentamicin cement is used routinely in joint replacement; this is also controversial. Antibiotic-soaked Dacron® vascular grafts are used in vascular surgery.

Antimicrobial stewardship

Antimicrobial stewardship is the practice of monitoring and improving the appropriate use of antibiotics by promoting best practice in the choice of regimen, duration, and route. Inappropriate use includes unnecessarily broad agents, unwarranted prophylaxis, and failing to administer by the route appropriate for the indication. Such use may lead to avoidable complications such as *C. difficile* diarrhoea, promotes the development of antibiotic resistance, and increases costs. The increase in prevalence of extended-spectrum β-lactamase (ESBL) organisms and the development of metallo-β-lactamase-1 (New Delhi metallo-β-lactamase-1, NDM-1) and other carbapenemase-mediated resistance raise the spectre of a return to a 'pre-antibiotic era', in which increasing resistance is not matched by the release of new drugs. Such concerns have prompted health systems across the world to promote stewardship interventions (e.g. the 'Start smart, then focus' toolkit in the UK). Evidence suggests that, just as the use of broad-spectrum agents promotes resistance, so changing prescribing practices to narrower agents is associated with a decline in resistant organisms such as MRSA.

Stewardship programmes

Successful implementation of such programmes requires leadership from senior hospital management and dedicated time from enthusiastic infection specialists and pharmacists. The UK Department of Health (DoH) recommends every hospital have an antibiotic prescribing and management group,

publish treatment and prophylaxis guidelines, and ensure good practice in prescribing. A typical stewardship programme includes:

- guidance on when to start antibiotics and locally developed treatment guidelines that balance the use of focused-spectrum agents with clinical safety;
- education of the importance of taking appropriate cultures prior to initiating therapy, so that a switch can be made from broad empirical therapy with confidence;
- regular review of the diagnosis (are antibiotics really required?), antibiotic given (switch to narrower agent once culture results available?), route (can a switch to oral be made?), and stop date (shortest possible course);
- rigorous enforcement of single-dose surgical prophylaxis guidelines;
- bedside review of those patients on broad agents by infection specialists to assess clinical indication and need;
- audit of antibiotic use to identify areas requiring specific interventions.

The UK 5-year antimicrobial resistance strategy 2013–2018

This initiative spans government agencies, including environmental and animal health. The aims are to slow the development and spread of antimicrobial resistance through improving understanding of resistance, promoting stewardship to conserve the effectiveness of existing treatments, and stimulate the development of new agents, novel therapies, and diagnostics.

Guidelines

Infectious Diseases Society of America (IDSA) stewardship guidelines: www.idsociety.org/stewardship_policy/.

UK 'Start smart, then focus': www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus.

Outpatient parenteral antimicrobial therapy

OPAT refers to the administration of IV antibiotics to those patients who require them but are otherwise well enough to remain in the community. Patients may attend an outpatient unit each day, or community teams may visit them at home to administer treatment.

The drive to reduce health costs has seen a rapid increase in OPAT, as health systems look for ways to avoid hospital admissions, reduce length of stay, and reduce health care-associated infections (HCAIs). Patients inevitably receive less supervision than they would as inpatients, and it is important that they are carefully selected and OPAT programmes have rigorous clinical oversight.

OPAT programme structure

Several national guidelines exist—all highlight the following key features.

- The team should have a medical lead, an infection specialist, an antimicrobial pharmacist, and a specialist nurse with expertise in IV drug administration and vascular access device management.
- Every patient should have a management plan agreed between the OPAT service and the referring specialty, with clearly defined lines of responsibility. Any primary care physician and community service would be kept fully informed, and systems should exist for urgent assessment or readmission, should it be required, while being managed by the service.
- Patient selection criteria should be well defined, and each patient assessed before acceptance. Criteria include physical nature of residence, accessibility/safety of visiting nurses, suitability and safety of any IV access device, and storage and safety of any prescribed medications in the home.
- The first dose should be administered by a professional competent and equipped to manage anaphylaxis. Records must be kept of drug administration.
- While on therapy, patients should be reviewed daily by a nurse or similar, with a view to oral switch. Patients should be reviewed weekly in a multidisciplinary team meeting. Those receiving extended therapy should be seen by a specialist nurse or doctor at agreed intervals and have appropriate blood tests performed.
- Data should be collected prospectively for the purposes of audit. This should be reviewed to detect issues relating to, for example, line infection, readmission, and drug reactions.

Guidelines

Chapman AL, Seaton RA, Cooper MA, *et al*. BSAC/BIA OPAT Project Good Practice Recommendations Working Group. (2012). Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. *J Antimicrob Chemother*. **67**:1053–62.

Tice AD, Rehm SJ, Dalovisio JR, *et al*.; IDSA. (2004). Practice guidelines for outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. **38**:1651–71.

Chapter 2

Antibiotics

Penicillins

Penicillin was discovered by Alexander Fleming in 1928 but did not become widely available until the 1940s. The penicillins are closely related compounds comprising a β-lactam ring, a five-membered thiozolidine ring, and a side chain (see Fig. 2.1). The ring structures are essential for antibacterial activity, and the side chain determines the spectrum and pharmacological properties. Most penicillins in current use are semi-synthetic derivatives of 6-aminopenicillic acid. They inhibit bacterial cell wall synthesis and are thus bactericidal.

Classification

- Group 1—benzylpenicillin and its long-acting parenteral forms.
- Group 2—orally absorbed penicillins, e.g. phenoxymethylpenicillin.
- Group 3—antistaphylococcal penicillin, e.g. meticillin, flucloxacillin.
- Group 4—extended-spectrum penicillins, e.g. amoxicillin.
- Group 5—antipseudomonal penicillins, e.g. ticarcillin, piperacillin.
- Group 6—β-lactamase-resistant penicillins.

Mode of action

The penicillins inhibit cell wall synthesis by binding to PBPs and inhibiting transpeptidation of peptidoglycans.

Resistance

Bacteria may become resistant to penicillins by a number of mechanisms:

- destruction of the antibiotic by β-lactamases (➔ see β-lactamases, pp. 35–7)—this is the commonest mechanism;
- failure to penetrate the outer membrane of Gram-negative bacteria;
- efflux across the outer membrane of Gram-negative bacteria;
- low-affinity binding of antibiotic to target PBPs.

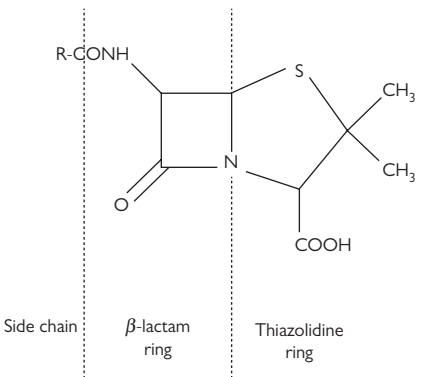

Fig. 2.1 Structure of penicillin.

Some bacteria may display >1 resistance mechanism, e.g. in MRSA, the *mecA* gene encodes an additional PBP (i.e. altered target site), and most also produce a β-lactamase.

Clinical use

- Benzylpenicillin is used in infections due to group A and group B streptococci; meningitis due to *S. pneumoniae* (if penicillin-susceptible) and *Neisseria meningitidis,* streptococcal and enterococcal endocarditis, neurosyphilis.
- Aminopenicillins are used in respiratory tract infections, endocarditis, meningitis, and urinary tract infections (UTIs) caused by susceptible organisms, and treatment of *H. pylori*.
- Extended-spectrum and antipseudomonal penicillins are used in infections due to resistant Gram-negative bacteria, usually in combination with an aminoglycoside.
- Phenoxymethylpenicillin is also used prophylactically to prevent recurrent rheumatic fever, secondary cases in outbreaks of GAS disease, and pneumococcal and *H. influenzae* infections in asplenic patients.

Pharmacology

- Penicillins differ markedly in their oral absorption (phenoxymethylpenicillin 60%, amoxicillin 75%, antipseudomonal penicillins 0%).
- They vary in their degree of protein binding, and metabolism is minimal.
- They are rapidly excreted by renal tubular cells; excretion may be blocked by probenecid. Dose modification may be required in renal failure.

Toxicity and side effects

- Allergic reactions (skin rashes, serum sickness, delayed hypersensitivity)—occur in <10% of those exposed. Anaphylactic reactions are rare (0.004–0.4%).
- GI—diarrhoea, enterocolitis (2–5%, usually ampicillin).
- Haematological—haemolytic anaemia, neutropenia; thrombocytopenia (1–4%).
- Laboratory—elevated transaminases (usually flucloxacillin), electrolyte abnormalities (hypernatraemia, hypo- or hyperkalaemia).
- Renal—interstitial nephritis, haemorrhagic cystitis.
- Central nervous system (CNS)—encephalopathy or seizures are rare, but may occur in renal failure or if high, prolonged doses of penicillin are used.

Cephalosporins

Giuseppe Brotzu first demonstrated the antimicrobial activity of culture filtrates of the mould *Cephalosporium acremonium* in 1945. However, the cephalosporin class of antibiotics did not become widely used for another 20 years. Cephalosporins consist of a β-lactam ring and a six-membered dihydrothiazine ring modified at certain positions to produce different compounds. Most available cephalosporins are semi-synthetic derivatives of cephalosporin C.

Classification

The classification into 'generations' is the most commonly used with each successive generation acquiring better Gram-negative activity, usually at the expense of some Gram-positive, until more broad-spectrum activity appears in generations 4 and 5. Not every country agrees on which agent belongs in which generation.

- First generation—primarily active against Gram-positive bacteria, e.g. cefazolin, cefalotin, cefradine, cefalexin.
- Second generation—enhanced activity against Gram-negative bacteria, with varying degrees of activity against Gram-positive bacteria, e.g. cefuroxime, cefamandole, cefaclor. The cephamycin group (e.g. cefotetan and cefoxitin) have additional anaerobic activity against e.g. *Bacteroides fragilis*.
- Third generation—markedly increased activity against Gram-negative bacteria, e.g. cefotaxime, ceftriaxone, ceftazidime (NB. poor activity against Gram-positives), cefdinir, cefixime, cefpodoxime.
- Fourth generation—broad spectrum of activity against Gram-positive cocci, and Gram-negative bacteria, including *Pseudomonas* spp., e.g. cefepime, cefpirome.
- Fifth generation—active against MRSA, e.g. ceftaroline (no pseudomonal or vancomycin-resistant enterococci (VRE) activity) and ceftobiprole (active against *Pseudomonas* and enterococci).

Mode of action

They inhibit cell wall synthesis by binding to PBPs and inhibiting transpeptidation of peptidoglycans. They are bactericidal and exhibit significant post-antibiotic effect against Gram-positive (but not Gram-negative) bacteria.

Resistance

- Due to: destruction of the antibiotic by β-lactamases (➔ see β-lactamases, pp. 35–7), reduced penetration through the outer membrane of Gram-negative bacteria, and enhanced efflux or alteration in PBP target, resulting in reduced-affinity binding.
- *Listeria*, 'atypical' organisms (*Mycoplasma, Chlamydia*), MRSA and enterococci ('LAME') were considered intrinsically resistant to cephalosporins—however, some fifth-generation agents have activity against the latter two.

Clinical use

- First generation—staphylococcal and streptococcal skin and soft tissue infections, UTIs.
- Second generation—severe community-acquired pneumonia (CAP), otitis media, sinusitis, streptococcal pharyngitis, early Lyme disease.
- Cephamycins—intra-abdominal, pelvic, and gynaecological infections, infected decubitus ulcers, diabetic foot infections, mixed aerobic–anaerobic soft tissue infections.
- Third generation—penicillin-resistant pneumococci, meningitis, URTIs and lower respiratory tract infections (LRTIs), sinusitis, otitis media, nosocomial infections caused by Gram-negative bacilli, *Neisseria gonorrhoeae*, chancroid, Lyme disease, typhoid, severe *Shigella* spp. and

Box 2.1 CAUTION!

The second- and third-generation cephalosporins are susceptible to inactivation by inducible β-lactamases (➔ see β-lactamases, pp. 35–7). They should never be used to treat organisms that may have these enzymes, e.g. *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii, Acinetobacter* spp., *Proteus vulgaris, Providencia* spp., *Morganella morganii* (ESCAPPM).

non-typhoidal *Salmonella* infection, outpatient antibiotic therapy for endocarditis and osteomyelitis.
- Fourth generation—role not yet clear, but effective in severe Gram-negative infections. Active against *P. aeruginosa, Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp.

Pharmacology

May be given PO, IV, or IM. Fourth-generation drugs are all parenteral. Oral preparations have 80–95% bioavailability. Protein binding is variable (10–98%). Drugs are largely confined to the extracellular compartment. Poor cerebrospinal fluid (CSF) penetration, unless meningeal inflammation. Cross the placenta. Most drugs are not metabolized, except cefotaxime and cealothin which are metabolized in the liver. Most drugs are excreted by the kidneys. Ceftriaxone and cefoperazone are excreted by the biliary system (see Box 2.1).

Toxicity and side effects

- Hypersensitivity—rash (1–3%), urticaria and serum sickness (<1%), anaphylaxis (0.01%).
- GI—diarrhoea (1–19%), nausea and vomiting (1–6%), transient hepatitis (1–7%), biliary sludging (ceftriaxone).
- Haematological—eosinophilia (1–10%), neutropenia, thrombocytopenia, clotting abnormalities, platelet dysfunction, haemolytic anaemia.
- Renal—interstitial nephritis.
- CNS—seizures.
- False-positive laboratory tests—Coombs' test, glycosuria, serum creatinine.
- Other—drug fever, disulfiram-like reaction, phlebitis.

β-lactamases

β-lactamases are enzymes that bind covalently to the β-lactam ring, hydrolyse it, and make the antibiotic ineffective. Emergence of resistance to β-lactam antibiotics began even before penicillin was widely available, with the first β-lactamase (penicillinase) being described in *Escherichia coli* in 1940. This was followed by the emergence of resistance in *S. aureus*, due to plasmid-encoded penicillinase. Many genera of Gram-negative bacilli possess naturally occurring chromosomally mediated β-lactamases (AmpC); these enzymes are thought to have evolved from PBPs, to which they are very similar. The first plasmid-mediated β-lactamase in Gram-negative

bacteria TEM-1 was described in 1960. Within a few years, it had spread worldwide and was found in many different species. Over the past 20 years, many antibiotics have been developed to be resistant to these β-lactamases. However, with each new class of drugs, new β-lactamases have emerged.

Classification

There are two classification systems for β-lactamases.

- Molecular (Ambler)—four classes (A to D) based on the nucleotide/amino acid sequences of the enzymes:
  - classes A, C, and D are serine β-lactamases;
  - class B are zinc-dependent enzymes (metallo-β-lactamases, MBLs) that hydrolyse the β-lactam ring by a different mechanism.
- Functional (Bush–Jacoby–Medeiros)—three groups, each with subgroups:
  - group 1 β-lactamases are cephalosporinases that are not inhibited by clavulanic acid. They correspond to Ambler group C;
  - group 2 β-lactamases are penicillinases and/or cephalosporinases that are inhibited by clavulanic acid. This group corresponds to Ambler groups A and D, and includes the TEM and SHV enzymes;
  - group 3 β-lactamases are zinc-dependent (MBLs) and are not inhibited by clavulanic acid. They correspond to Ambler group B;
  - group 4 is no longer used—it included enzymes that would have been included in one of the other groups, if more information had been available.

AmpC β-lactamases

These are chromosomally mediated β-lactamases that are active against third-generation cephalosporins and are not inhibited by clavulanic acid. They fall into molecular group C/functional group 1. They are found in the ESCAPPM group of organisms, e.g. *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii, Acinetobacter* spp., *Proteus vulgaris, Providencia* spp., and *Morganella morganii*. The use of third-generation cephalosporins to treat these infections results in the selection of stably derepressed mutants that hyperproduce AmpC, and has been associated with clinical failure. These infections are therefore usually treated with carbapenems.

Extended-spectrum β-lactamases

These are β-lactamases which are capable of conferring bacterial resistance to the penicillins, first-, second-, and third-generation cephalosporins, and aztreonam (but not the cephamycins or carbapenems) by hydrolysis of these antibiotics, and which are inhibited by β-lactamase inhibitors such as clavulanic acid. They fall into functional groups 2be and 2d. ESBLs are most commonly found in *E. coli* and *Klebsiella pneumoniae*, but have been described in many other Gram-negative bacilli. Most ESBLs are derivatives of the TEM and SHV enzymes (see below).

- TEM β-lactamases—TEM-1 is the commonest β-lactamase in Gram-negative bacteria and is able to hydrolyse penicillins and early-generation cephalosporins. TEM-2 has a similar spectrum. TEM-3 was the first ESBL, reported in 1989. Since then, over 160 TEM enzymes have been described. Most of these are inhibited by clavulanic acid, but some

inhibitor-resistant variants exist, particularly in Europe. TEM enzymes are commonest in *E. coli* and *K. pneumoniae*, but are increasingly found in other species of Gram-negative bacilli.

- SHV β-lactamases—the SHV-1 β-lactamase is most commonly found in *K. pneumoniae* and accounts for ≤20% of ampicillin resistance in this species. Unlike TEM, there are relatively few SHV-1 derivatives.
- CTX-M β-lactamases—this family of plasmid-mediated β-lactamases preferentially hydrolyses cefotaxime. They have been found in *Salmonella enterica* serovar Typhimurium and *E. coli*, as well as other enterobacteria. These enzymes are quite different to the TEM and SHV enzymes, and show greater similarity to chromosomal AmpC enzyme of *Kluyvera ascorbata*, suggesting CTX-M may have originated from this species. CTX-M β-lactamases have previously been associated with outbreaks in Europe, South America, and Japan, although they are now reported worldwide.
- OXA β-lactamases—these are characterized by their high hydrolytic activity against oxacillin and cloxacillin, and are poorly inhibited by clavulanic acid. They belong to molecular group D/functional group 2d. OXA-type ESBLs are mainly found in *P. aeruginosa* but have been detected in other Gram-negative bacteria. More recently, non-ESBL OXA derivatives have been described.
- Other ESBLs—a number of ESBLs that are unrelated to the established families of ESBLs have been described, e.g. PER-1, PER-2, VEB-1, GES, BES, TLA, SFO, and IBC.

ESBL detection methods

In general, ESBL detection methods use a β-lactamase inhibitor (clavulanate) in combination with an oximino-cephalosporin, e.g. ceftazidime or cefotaxime. Clavulanate inhibits the ESBL, thereby reducing the level of resistance to the cephalosporin. A number of methods exist, e.g. Jarlier double disc method, Etest® for ESBLs.

β-lactamase inhibitors

β-lactamase inhibitors are clavulanic acid and penicillanic acid sulfone derivatives. They have weak antibacterial activity but are potent inhibitors of many β-lactamases, e.g. penicillinases produced by *S. aureus, H. influenzae, Moraxella catarrhalis*, and *Bacteroides* spp., and of TEM and SHV β-lactamases produced by *Enterobacteriaceae*. They can restore the antibacterial activity of certain antibiotics, e.g. amoxicillin, ampicillin, piperacillin, mezlocillin, and cefoperazone. Three β-lactamase inhibitors are in clinical use: clavulanic acid, sulbactam, and tazobactam. All are only available in combination with a β-lactam antibiotic; the antibiotic spectrum is determined by the companion antibiotic. Although there are minor differences in potency, activity, and pharmacology between the three compounds, they can be considered therapeutically equivalent (except for some *Klebsiella* spp. where clavulanate inhibits isolates resistant to sulbactam and tazobactam).

Co-amoxiclav

- Clavulanate is a potent inhibitor of many plasmid-mediated β-lactamases and a weak inducer of some chromosomal β-lactamases.
- It is available as a combination with amoxicillin and used for the treatment of a wide range of infections where β-lactamase-producing organisms may be present. Examples include otitis media, sinusitis, pneumonia, skin and soft tissue infections, diabetic foot infections, and bite infections.
- It is available as oral or parenteral formulations. In the oral formulation, the ratio of amoxicillin to clavulanic acid is 2:1, e.g. 250mg/125mg, whereas, in the IV formulation, it is 5:1, e.g. 1000mg/200mg.
- Side effects are similar to ampicillin. Cholestatic jaundice may occur during/after therapy and is six times commoner than with amoxicillin alone.

Ticarcillin/clavulanic acid

- This combination is useful against infections caused by *Pseudomonas* spp. and *Proteus* spp.
- It has been used for the treatment of pneumonia, intra-abdominal infections, gynaecological infections, skin and soft tissue infections, and osteomyelitis.
- It is only available in parenteral form and is given IV.
- Side effects are similar to those of other β-lactams. Cholestatic jaundice may also occur because of the clavulanic acid component.

Ampicillin–sulbactam

- Sulbactam is 6-desaminopenicillin sulfone. It has a broader spectrum of activity but is less potent than clavulanic acid.
- In the USA, it is available as a combination with ampicillin and is given IV.
- It is used for the treatment of skin and soft tissue infections, intra-abdominal infections, and gynaecological infections caused by β-lactamase-producing bacteria. It has also recently been used to treat carbapenem-resistant *A. baumanii* infections.
- Side effects are similar to those of ampicillin.

Piperacillin–tazobactam

- Tazobactam is penicillanic acid sulfone β-lactamase inhibitor, with a similar structure to that of sulbactam. Its spectrum of activity is similar to that of sulbactam, but its potency is comparable to clavulanic acid.
- It is available as a combination with piperacillin (an antipseudomonal penicillin) and is given parenterally.
- It has a broad spectrum of activity and is used in the treatment of pneumonia (especially *P. aeruginosa*), skin and soft tissue infections, intra-abdominal infections, UTIs, polymicrobial infections, bacteraemia, and febrile neutropenia (in combination with an aminoglycoside).
- Side effects are similar to those of piperacillin.

Carbapenems

The carbapenems are β-lactam antibiotics derived from thienamycin, a compound produced by *Streptomyces cattleya*. Three carbapenems are licensed for use in the UK: imipenem, meropenem, and ertapenem. Other drugs in the same class include panipenem, doripenem, and faropenem.

Mode of action

These agents show high affinity to most high-molecular-weight PBPs of Gram-positive and Gram-negative bacteria. Carbapenems, particularly imipenem, traverse the outer membrane of Gram-negative bacteria through different outer membrane proteins (OprD) than those that are used by penicillins and cephalosporins (OmpC and OmpF). They also have excellent stability to β-lactamases. Consequently, carbapenems have the broadest antibacterial spectrum of all the β-lactam antibiotics. Imipenem is slightly more active against Gram-positive bacteria, whereas meropenem and ertapenem are slightly more active against Gram-negative species. Meropenem is the most active against *P. aeruginosa*. Ertapenem has poor activity against *P. aeruginosa* and *Acinetobacter* spp.

Resistance

Resistance is due to one of four mechanisms: the production of a low-affinity PBP target, reduced outer membrane permeability due to the absence of OprD in Gram-negative bacteria, efflux of the drug in Gram-negative bacteria, or the production of β-lactamases (➔ see β-lactamases, pp. 35–7) that hydrolyse carbapenems (carbapenemases). Carbapenem resistance in *Enterobacteriaceae* may be due to a combination of porin loss PLUS an ESBL or AmpC enzyme (such strains rarely spread) OR an acquired carbapenemase (such a strain being more likely to spread, and often occurring in strains already resistant to many antibiotics). For a summary of carbapenemases, see Table 2.1.

Clinical use

- Carbapenems may be used to treat a wide variety of severe infections, e.g. bacteraemia, pneumonia, intra-abdominal infections, obstetric and gynaecological infections, complicated UTIs, and soft tissue and bone infections.
- Imipenem and meropenem are most appropriate for treatment of infections caused by the cephalosporin-resistant AmpC-producing organisms, e.g. *Enterobacter* spp., *Serratia* spp., *C. freundii*, *Acinetobacter* spp., *P. vulgaris*, *Providencia* spp., *M. morganii* (the ESCAPPM group).
- Imipenem and meropenem are also used for the treatment of serious infections, e.g. patients with polymicrobial infections, febrile neutropenia, and nosocomial infections such as those caused by *P. aeruginosa* and *Acinetobacter* spp.
- Meropenem is also licensed for the treatment of bacterial meningitis—imipenem should not be used because of its propensity to cause seizures.
- Ertapenem has similar uses to those of imipenem and meropenem, but cannot be used in infections caused by *P. aeruginosa* and *Acinetobacter* spp. Its long plasma half-life means that it can be administered once daily, making it useful for OPAT.

Table 2.1 A summary of the main carbapenemases

Enzyme	Class	Characteristics
IMP-type	Metallo (class B)	Plasmid-mediated, at least 17 varieties, originated in Japan in 1990s in enterics. Now worldwide. Also found in *Pseudomonas* and *Acinetobacter*
VIM	Verona Integron-encoded metallo (class B)	Originally from Italy (1999), at least ten types, now wide geographic distribution. Mainly found in *P. aeruginosa* and *Pseudomonas putida*, only rarely in *Enterobacteriaceae*
OXA	Oxacillinase (class D)	Occurs mainly in *Acinetobacter*. Also OXA-48 *K. pneumoniae* in the Middle East, North Africa, and imported into the UK. Both plasmid and clonal spread
KPC	*K. pneumoniae* carbapenemase (class A)	Ten variants, KPC-2 to KPC-11 which differ by one or two amino acid substitutions. Also clonal spread, including global *K. pneumoniae* ST258 lineage
CMY	Class C	First class C carbapenemase, isolated from *Enterobacter aerogenes* in 2006 on plasmid pYMG-1
SME, IMI, NMC, CcrA	Class A	Little clinical significance at present
NDM-1	New Delhi metallo-β-lactamase	Described originally in New Delhi in 2009. Mainly plasmid spread in *E. coli* and *K. pneumoniae*

Pharmacology

- Imipenem, meropenem, and ertapenem have poor oral absorption and are given parenterally.
- Imipenem and meropenem are pharmacologically similar, with a plasma half-life of 1h, whereas ertapenem has a plasma half-life of 4h, which permits once-daily dosing.
- All carbapenems are widely distributed and penetrate inflamed meninges.
- All are renally excreted and require dose modification in renal failure.
- Imipenem is a substrate for renal dehydropeptidase-1 (DHP-1) enzyme and is therefore co-administered with cilastatin, a DHP-1 inhibitor.

Toxicity and side effects

- Carbapenems are generally well tolerated.
- β-lactam allergic reactions are the commonest side effects, e.g. rash, urticaria, immediate hypersensitivity, and cross-reactivity with penicillin.
- Imipenem causes nausea (if infused too quickly) and can cause seizures.

Carbapenemases

Carbapenem antibiotics (see Carbapenems, pp. 39–40) are the cornerstone agents for treating ESBL infection. The emergence of carbapenem-hydrolysing β-lactamases has prompted great concern. Enzymes have been identified belonging to classes A and B (the MBLs) and can be chromosomally or plasmid-mediated, the latter facilitating transmission between strains and species. *K. pneumoniae* carbapenemase (KPC) is the most clinically important of class A carbapenemases—they are plasmid-mediated and confer resistance to all β-lactams. NDM-1, a novel MBL, was first described in 2009 in a European patient hospitalized in India with a *K. pneumoniae* infection. It has been identified in other *Enterobacteriaceae*, including *E. coli* and *Enterobacter*. In general, bacteria carrying NDM-1 are sensitive to colistimethate sodium or tigecycline.

Monobactams

The monobactams are monocyclic β-lactam antibiotics produced by some bacteria (e.g. *Chromobacterium violaceum*). They are only active against Gram-negative bacteria.

Aztreonam

- Aztreonam is the only commercially available compound.
- It is active against most *Enterobacteriaceae, H. influenzae*, and *Neisseria* spp. *Stenotrophomonas maltophilia, Burkholderia cepacia*, and many *Acinetobacter* spp. are resistant. Some strains of *P. aeruginosa, Enterobacter cloacae*, and *C. freundii* are resistant.
- Aztreonam passes through the outer membrane and binds to PBP3 of Gram-negative bacteria. It is resistant to hydrolysis by most β-lactamases, apart from AmpC β-lactamases.
- Aztreonam is not absorbed PO and is given IV or IM. It is widely distributed and penetrates inflamed meninges. It is mainly renally excreted and requires dose modification in renal failure.
- It is used for the treatment of a variety of infections, e.g. UTIs, pneumonia, septicaemia, skin and soft tissue infections, intra-abdominal infections, gynaecological infections, and wound and burn infections.
- Aztreonam should never be used alone as empiric therapy, as it has no activity against Gram-positive organisms.
- Side effects are similar to those of the other β-lactams, except for hypersensitivity which does not occur.

Other cell wall agents

Bacitracin

Bacitracin binds to isoprenyl phosphate and prevents dephosphorylation of the lipid carrier that transports the cell wall building block across the membrane. Without dephosphorylation, the native compound cannot be regenerated for another round of transfer. Similar reactions in eukaryotic

cells may be why this agent is so toxic, and it is therefore used topically. It is also used to identify GAS (bacitracin-resistant) in the diagnostic laboratory.

Fosfomycin

Fosfomycin inhibits pyruvyl transferase, and therefore formation of *N*-acetylglucosamine from *N*-acetylmuramic acid. It is a naturally occurring antibiotic with a fairly broad spectrum, particularly against Gram-negative rods (GNRs). It is mainly used to treat UTIs.

Cycloserine

This drug is often part of the second-line regimen for drug-resistant TB. It is a structural analogue of *D*-alanine, and acts on alanine racemase and synthetase to inhibit the synthesis of terminal *D*-alanyl-*D*-alanine. It thus prevents formation of the pentapeptide chain of muramic acid (➔ see Antituberculous agents, second line, pp. 73–4).

Isoniazid and ethambutol

These are first-line drugs used in the treatment of TB. They interfere with mycolic acid synthesis in mycobacterial cell walls (➔ see Antituberculous agents, first line, pp. 71–3).

Glycopeptides

The glycopeptide antibiotics vancomycin and teicoplanin are bactericidal against most Gram-positive bacteria. Vancomycin was first isolated from *Nocardia orientalis* and introduced into clinical practice in 1958. Teicoplanin was obtained from *Actinoplanes teichomyceticus* in 1978 and is available in Europe and Asia, but not in the USA.

Mode of action

Glycopeptides inhibit cell synthesis by binding to the *D*-alanyl-*D*-alanine tail of the muramyl pentapeptide. This complex cannot be processed by the enzyme glycosyltransferase, inhibiting the incorporation of murein monomers (*N*-acetylmuramic acid and *N*-acetylglucosamine) into the growing peptidoglycan chain.

Antimicrobial activity

Glycopeptides have broad activity against Gram-positive organisms, e.g. staphylococci, *E. faecalis, S. pneumoniae*, groups A, B, C, and G streptococci, *Streptococcus bovis, Streptococcus mutans*, viridans group streptococci, *Listeria monocytogenes, Bacillus* spp., *Corynebacterium* spp., *Peptostreptococcus* spp., *Actinomyces* spp., *Propionibacterium* spp., and most *Clostridium* spp. Glycopeptides show no activity against Gram-negative species (except non-gonococcal *Neisseria* spp.). The MICs of teicoplanin against coagulase-negative staphylococci (CoNS) are more variable than that of vancomycin.

Resistance

Vancomycin resistance may be intrinsic or acquired.

- Intrinsic vancomycin resistance occurs in *Leuconostoc, Pediococcus, Lactobacillus*, and *Erysipelothrix rhusiopathiae*. Intrinsic teicoplanin resistance is seen in *Staphylococcus haemolyticus*.

Table 2.2 Vancomycin resistance in enterococci and staphylococci

	VanA	VanB	VanC	VanD	VanE	VanG
Vanc MIC	64–>500	4–>500	2–32	64–128	16	12–16
Teic MIC	16–>500	0.5–2	0.5–2	4–64	0.5	0.5
Expression	Inducible	Inducible	Constitutive, inducible	Constitutive	Inducible	
Location	P, C	P, C	C	C	C	C
Species	*E. faecalis*, *E. faecium*, *S. aureus*	*E. faecalis*, *E. faecium*	*E. gallinarum*, *E. casselflavius*, *E. flavescens*	*E. faecium*	*E. faecalis*	*E. faecalis*

C, chromosome; MIC, minimum inhibitory concentration (microgram/mL); P, plasmid; Teic, teicoplanin; Vanc, vancomycin.

- Enterococci—six types of glycopeptide resistance have been described (VanA, VanB, VanC, VanD, VanE, and VanG), named on the basis of their ligase genes (*vanA*, *vanB*, etc.; see Table 2.2). These result in the formation of a peptidoglycan precursor with decreased affinity for glycopeptides. Resistance may be intrinsic (e.g. in *Enterococcus gallinarum*, *Enterococcus casseliflavus*) or acquired (e.g. in *E. faecium* and *E. faecalis*).
- *S. aureus*—the first clinical isolate of *S. aureus* with diminished susceptibility to vancomycin was reported in Japan in 1997. This is referred to as a vancomycin-intermediate *S. aureus* (VISA) or glycopeptide-intermediate *S. aureus* (GISA). VISA isolates have a thickened cell wall which may prevent glycopeptides from reaching their target sites. In 2002, two isolates of truly vancomycin-resistant *S. aureus* (VRSA) were reported, both of which carried the *vanA* gene, suggesting horizontal transfer of this gene from enterococci.
- *S. pneumoniae*—vancomycin tolerance has recently been reported.

Clinical use

Glycopeptides are used to treat the following conditions:

- severe infections caused by MRSA;
- meningitis due to penicillin-resistant *S. pneumoniae*;
- *C. difficile*-associated diarrhoea (oral vancomycin);
- febrile neutropenia;
- continuous ambulatory peritoneal dialysis (CAPD) peritonitis;
- endophthalmitis;
- empiric treatment of intravascular catheter-related infections and cerebrospinal fluid (CSF) shunt infections.

Pharmacology

- Vancomycin is usually given intravenously but may also be given orally, intraperitoneally, intrathecally or intraocularly. It is widely distributed but has poor CSF penetration in the absence of meningeal inflammation. Vancomcyin is excreted unchanged in the kidneys, and dose reduction

is required in renal impairment. Vancomycin shows time-dependent killing: if the trough level is too high, it is better to reduce the dose rather than increase the dosing interval.
- Teicoplanin is usually administered IV and IM, but may also be given intraperitoneally. It has a long plasma half-life (83–168h), enabling daily dosing. Teicoplanin has better bone penetration than vancomcyin. It is excreted by the kidneys.

Toxicity and side effects

Toxicity is commoner with vancomycin than teicoplanin.
- Ototoxicity is rare, unless there is renal impairment.
- Nephrotoxicity occurs with high doses and is often associated with concomitant aminoglycoside usage.
- Infusion-related reactions can occur, e.g. 'red man syndrome' with rapid infusion of vancomcyin.
- Others, e.g. neutropenia, thrombocytopenia, rashes, drug fever.

Glycopeptide monitoring

Basic principles of glycopeptide monitoring are described on ➔ pp. 42–4. Please consult your hospital guidelines, antibiotic pharmacist, or infection specialist for specific advice.
- Recommended initial dose of vancomycin or teicoplanin depends on the type of infection, patient weight, and renal function. Loading doses (based on actual body weight) are commonly given, if CrCl >20mL/min.
- Vancomycin trough (pre-dose) levels are usually monitored to reduce the risk of nephrotoxicity and guide future dosing. Always review any other nephrotoxic drugs your patient is taking (e.g. gentamicin) (see Table 2.3).
- Teicoplanin trough (pre-dose) levels are usually monitored in severe infections to ensure therapeutic levels. Monitoring is not needed for toxicity (see Table 2.4).

Table 2.3 Interpretation of vancomycin pre-dose (trough) levels

<10mg/L	Subtherapeutic	Check sample timing. If a true sample, increase dose (usually by 500mg increments, either as once daily (od) or in divided doses)
10–20mg/L	Optimum dose*	Continue on current dose; re-assay 1–2 times a week if no change in renal function
20–25mg/L	Above recommended target level	Reassessment/extend dosing interval, e.g. from twice daily (bd) to od. Re-assay after third dose
>25mg/L	Above recommended target level	Omit further dosing until level <20mg/L. Reassessment/extend dosing interval

* For severe infections (e.g. MRSA pneumonia, osteomyelitis, endocarditis, and bacteraemias), many experts aim for a target concentration of 15–20mg/L.

Table 2.4 Interpretation of teicoplanin pre-dose (trough) levels

<20mg/L	Subtherapeutic level, especially if severe infections	Increase dose (usually by ~50%). Re-assay after five doses
20–60mg/L	Optimum dose	Continue on current dose, and re-assay in 1 month, if no change in renal function
>60mg/L	Above recommended target level	Reassess dose according to renal function. Consider reducing daily dose or extending the dosage interval (e.g. to every 48h)

- Information: always state the time of last dose, time of sample, and current dosing regimen, to aid interpretation of result.
- Timing of levels: vancomycin is usually monitored before the third dose (unless CrCl <10mL/min, then before second dose). Teicoplanin is usually monitored after 7 days of treatment.

Lipoglycopeptides

Dalbavancin, oritavancin, and telavancin are semi-synthetic lipoglycopeptides, not yet licensed in the UK. They have been developed to treat infections with multiresistant Gram-positive pathogens. The heptapeptide core (common to all glycopeptides) results in inhibition of cell wall synthesis (transglycosylation and transpeptidation), and the lipophilic side chain prolongs the half-life, helping to anchor the drug to the cell membrane. Telavancin and oritavancin also disrupt bacterial membrane integrity and increase membrane permeability, while oritavancin also inhibits RNA synthesis. All three agents are active *in vitro* against *S. aureus* (including MRSA), *Staphylococcus epidermidis, Streptococcus* spp., and VanB-VRE. Oritavancin is also active against VISA, VRSA, and VanA-VRE, while dalbavancin and telavancin are also active against VISA, but not against VanA-VRE or VRSA. These may be potential alternatives for complicated skin and skin structure infections, if cheaper options, such as vancomycin, have been ineffective or in cases of reduced vancomycin susceptibility or resistance. Dalbavancin is given once weekly which may facilitate outpatient treatment.

Fidaxomicin

Fidaxomicin is the fermentation product of the actinomycete *Dactylosporangium aurantiacum* subspecies *hamdenesis*. It is the first in a new class of macrocyclic antibiotics, and is bactericidal, poorly absorbed systemically, and more selective for *C. difficile*, with minimal disruption to normal gut flora. Evidence from two double-blind randomized controlled trials (RCTs) indicates it is non-inferior to vancomycin in curing patients with mild to severe *C. difficile* infection (CDI). It reduces the recurrence rate of CDI,

and its side effect profile is similar to oral vancomycin. There are no clinical trials comparing fidaxomicin to metronidazole. The National Institute for Health and Care Excellence (NICE) guidance in 2012 recommended considering fidaxomicin for patients with severe or recurrent CDI.[1] Consult an infection expert, and weigh up the potential benefits alongside the medical need, risks of treatment, and relatively high cost of fidaxomicin (see *Clostridium difficile* diarrhoea, pp. 654–6).

Reference

1 National Institute for Health and Care Excellence (2012). *Clostridium difficile infection: fidaxomicin*. Available at: http://www.nice.org.uk/advice/esnm1/chapter/Relevance-to-NICE-guidance-programmes.

Aminoglycosides

Streptomycin, produced by *Streptomyces griseus*, was the first aminoglycoside used in the initial treatment trials of TB in the 1940s. Today aminoglycosides remain an important part of the antibiotic arsenal. All aminoglycosides have an essential six-membered ring with amino group constituents (aminocyclitol). The term aminoglycoside results from glycosidic bonds between aminocyclitol and two or more sugars. They are active against many Gram-negative, and some Gram-positive, organisms. In the UK, the currently available aminoglycosides are: streptomycin, neomycin, kanamycin, paromomycin, gentamicin, tobramycin, amikacin, netilmicin, and spectinomycin. Other drugs (e.g. sisomicin, dibekacin, and isepamicin) are available in Japan and continental Europe.

Mode of action

Aminoglycosides bind to the A site of the 30S ribosomal subunit, resulting in a conformational change that interferes with mRNA translation and translocation, and hence inhibit protein synthesis. Avidity of binding varies between aminoglycosides. The transport of aminoglycosides into the cell by energy-dependent mechanisms (EDP-I and EDP-II) results in accumulation of high concentrations of the drug in the cell. The onset of cell death is coincident with the transition from EDP-I to EDP-II.

Resistance

Resistance to aminoglycosides may be intrinsic or acquired.

- Intrinsic resistance may be non-enzymatic or enzymatic:
  - anaerobes are unable to generate a sufficient electrical potential difference across the membrane and are intrinsically resistant;
  - mutations in the 16S ribosomal subunit can result in resistance to streptomycin in MTB;
  - methylating enzymes that modify 16S rRNA may cause intrinsic resistance; this has not yet been seen in clinical isolates.
- Acquired resistance may occur by a variety of mechanisms:
  - reduced drug uptake;
  - efflux pumps, e.g. activation of the Mex XY pump in *P. aeruginosa*;

- enzymatic modification of the drug may occur as a result of aminoglycoside-modifying enzymes (AMEs) that phosphorylate, acetylate, or adenylate exposed amino or hydroxyl groups. The enzymatically modified drugs bind poorly to ribosomes, resulting in high levels of resistance.

Clinical use

- Empiric therapy—aminoglycosides may be given as empiric therapy for serious infections suspected to be due to Gram-negative bacteria. Depending on the clinical indication, they are usually combined with a β-lactam, vancomycin, or an anaerobic agent.
- Specific therapy—once culture results are available, aminoglycosides may be useful for the specific treatment, e.g. infections due to *Pseudomonas* spp. or resistant Gram-negative species, endocarditis.
- Prophylaxis—aminoglycosides are sometimes used prophylactically, e.g. to prevent enterococcal endocarditis in 'at-risk' patients undergoing GU or GI procedures.
- Gentamicin is the most commonly used aminoglycoside in the UK. Its main use is in the empirical treatment of serious infections (e.g. septicaemia, febrile neutropenia, biliary sepsis, acute pyelonephritis, endocarditis). It is often incorporated into cement in orthopaedic procedures. Gentamicin drops are used in superficial eye infections and bacterial otitis externa.
- Amikacin is used in gentamicin-resistant infections, mycobacterial infections, or nocardiosis.
- Tobramycin is slightly better for *P. aeruginosa* than gentamicin, and may be used in CF patients.
- Neomycin is given PO for bowel sterilization pre-surgery or for selective decontamination of the digestive tract (➔ see Antimicrobial prophylaxis, pp. 25–7).
- Netilmicin is used in Gram-negative infections that are resistant to gentamicin.
- Streptomycin is used to treat TB, particularly in the developing world. It is sometimes used synergistically in enterococcal endocarditis (if there is gentamicin resistance).
- Spectinomycin is used to treat gonococcal infections.
- Paromomycin is used to treat cryptosporidiosis.

Pharmacology

- The aminoglycosides share a number of important characteristics (➔ see Pharmacodynamics, pp. 16–8):
  - concentration-dependent bactericidal activity;
  - significant PAE;
  - synergism particularly with cell wall-active agents.
- Aminoglycosides have poor oral absorption and are usually administered IV or IM. They may also be administered PO (e.g. neomycin, paromomycin), TOP, intrapleurally, intraperitonally, or intrathecally.

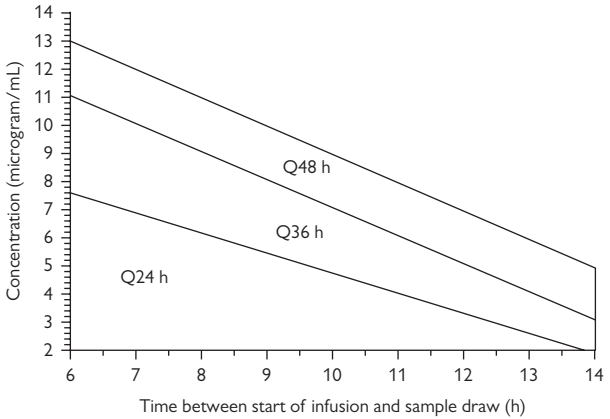

Fig. 2.2 Hartford nomogram for once-daily aminoglycosides.
Reproduced with permission from Nicolau *et al*. (1995). *Antimicrob Agents Chemother* **39**:650–5.

- Aminoglycosides are highly soluble with low protein binding, resulting in distribution in the vascular and interstitial compartments. CSF penetration is poor, apart from in neonates. Aminoglycosides are excreted unchanged in the urine (99%).
- Aminoglycosides may be given od or in multiple daily doses. od dosing is simpler and as efficacious as multiple dosing, and may lower the risk of drug-induced toxicity. The usual suggested dose of gentamicin is 5–7mg/kg/day. The dose is reduced in renal failure to 3mg/kg/day. Exceptions: children, pregnancy, burns, endocarditis. If patients need to continue therapy beyond 48h, trough drug levels should be monitored, and the dosing interval adjusted according to the Hartford nomogram (see Fig. 2.2).

Toxicity and side effects

- Nephrotoxicity is the commonest adverse effect (5–25%).
- Ototoxicity (cochlear and vestibular) may be irreversible.
- Neuromuscular blockade is rare.

Macrolides

The macrolides (erythromycin, clarithromycin, azithromycin) and the lincosamides (lincomycin and clindamycin), although chemically unrelated, have some similar properties such as antimicrobial activity, mechanisms of action, and resistance and pharmacology. The ketolides are a new class of antibiotics, derived from erythromycin, with activity against macrolide-resistant strains.

Erythromycin

- Erythromycin was derived from *Saccharopolyspora erythraea* in 1952. Erythromycin A is the active component. It consists of a 14-membered macrocyclic lactone ring attached to two sugars.
- Mode of action—inhibits RNA-dependent protein synthesis at the step of chain elongation by interacting with the peptidyl transferase site. It also inhibits the formation of the 50S ribosomal subunit.
- Resistance—there are four resistance mechanisms:
  - decreased outer membrane permeability, e.g. *Enterobacteriaceae, Pseudomonas* spp., *Acinetobacter* spp. are intrinsically resistant;
  - efflux pumps, e.g. *msr(A)* gene of *S. aureus* and *mef(A)* gene of *S. pneumoniae* and GAS;
  - alterations of 23S rRNA by methylation of adenine. This confers resistance to macrolides, lincosamides, and streptogramins type B, and is referred to as the MLS_B phenotype. It is encoded by *erm* (erythromycin ribosomal methylase) genes;
  - enzymatic inactivation by phosphotransferases, mediated by *mph* genes. Hydrolysis of the macrocyclic lactone is encoded by esterase genes *ere(A)* and *ere(B)* on plasmids.
- Clinical use—CAP, atypical pneumonia (e.g. *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila*), *Bordetella pertussis, Campylobacter* gastroenteritis.
- Pharmacology—given PO (stimulates GI motility) or IV. Widely distributed in tissues. Excreted in the bile and urine; some is inactivated in the liver.
- Toxicity and side effects—GI symptoms (nausea, vomiting, abdominal cramps, diarrhoea) are common; skin rash, fever, eosinophilia, cholestatic jaundice, transient hearing loss, QT prolongation, torsades de pointes, candidiasis, pseudomembranous colitis, infantile pyloric stenosis.

Clarithromycin

- Structure—14-membered ring with a methoxy group at position 6.
- Mode of action—same as erythromycin. More active than erythromycin against *S. pneumoniae*, GAS, MRSA, *M. catarrhalis*, and *L. pneumophila*. Also active against *Mycobacterium leprae, Mycobacterium* avium complex (MAC), and *Toxoplasma gondii*.
- Resistance—similar to erythromycin.
- Clinical use—similar to erythromycin. Treatment of MAC and other non-tuberculous mycobacterial (NTM) infections, *H. pylori* eradication, Lyme disease.
- Pharmacology—given PO or IV. Metabolized in the liver to active metabolites.

Azithromycin

- Structure—15-membered lactone ring (azalide).
- Mode of action—same as erythromycin. Greater activity against Gram-negative species than with erythromycin and clarithromcyin. Also active against MAC and *T. gondii*.
- Resistance—similar to erythromycin.

- Clinical use—similar to erythromycin. Also use for treatment of trachoma, *Babesia microti, Borrelia burgdorferi*, cryptosporidiosis.
- Pharmacology—given PO, but should be taken 1h before or 2h after food. Widely distributed in tissues, with a half-life of 2–4 days. Mostly not metabolized and excreted in the bile.
- Toxicity and side effects—similar to erythromycin.

Spiramycin

- Used in treatment of cryptosporidia and prevention of congenital toxoplasmosis.

Ketolides

Ketolides are a new class of antibiotics derived from erythromycin A that have increased potency against bacteria that have become resistant to macrolides, e.g. *S. pneumoniae* and *Streptococcus pyogenes*. Telithromycin is currently the only available drug.

Telithromycin

- Structure—a 14-membered ring with ketone, instead of l-cladinose, at position 3; this prevents induction of macrolide–lincosamide–streptogramin B (MLS_B) resistance (➔ see Lincosamides, pp. 51–2; see Box 2.2).
- Mode of action—similar to that of erythromycin.
- Resistance—this is uncommon, as ketolides are poor inducers of efflux pumps and MLS_B methylase genes. *S. aureus* strains with constitutive *erm* genes are resistant, whereas *S. pneumoniae* strains with constitutive *erm* genes remain sensitive.
- Toxicity and side effects—similar to clarithromycin and azithromycin. Reports of exacerbation of myasthenia gravis.
- Pharmacology—good oral absorption and bioavailability. Metabolized in the liver by CYP3A4.
- Clinical use—CAP, acute exacerbation of chronic obstructive pulmonary disease (COPD), tonsillitis, pharyngitis, and sinusitis.

Box 2.2 MLS_B resistance (also known as inducible resistance)

Macrolides, lincosamides, and streptogramin type B (MLS_B) antibiotics bind to closely related sites on the 50S ribosome of bacteria. One consequence is that some bacteria (e.g. staphylococci, streptococci, and enterococci) with inducible resistance to erythromycin also become resistant to the other MLS_B agents, in the presence of erythromycin. The methylase enzyme involved is not induced by lincosamides or streptogramins, which therefore remain active in the absence of macrolides. Over 20 *erm* genes encode the MLS_B resistance, and it is becoming commoner in GAS and pneumococci.

Lincosamides

This group of antibiotics includes lincomycin (not available in the UK) and clindamycin. Lincomycin was isolated from *Streptomyces lincolnensis* in 1962. Clindamycin, which was produced by the chemical modification of lincomycin, has better oral bioavailability and increased bacterial potency, compared with lincomycin. Although chemically unrelated to erythromycin, many of the biological properties of lincosamides are similar to the macrolides.

Mode of action

Lincosamides inhibit protein synthesis by interacting with the peptidyl transferase site of the 50S ribosomal subunit. They also inhibit the formation of the 50S ribosomal subunit. Clindamycin is highly active against anaerobes (e.g. *B. fragilis*), pneumococci, GAS, meticillin-sensitive *S. aureus* (MSSA), *T. gondii*, and *Plasmodium falciparum*.

Resistance

There are several resistance mechanisms.

- Alteration of 50S ribosomal proteins of the receptor site confers resistance to macrolides and lincosamides.
- Alteration in the 23S subunit by methylation of adenine results in the MLS_B phenotype (see Box 2.2) and confers resistance to macrolides, lincosamides, and type B streptogramins. This MLS_B phenotype is encoded by *erm* (erythromycin ribosomal methylase) genes.
- Inactivation by 3-lincomycin, 4-clindamycin 0-nucleotidyl transferase. This is plasmid-mediated and encoded by *linA* and *linA′* genes.
- Decreased membrane permeability in Gram-negative species, e.g. *Enterobacteriaceae, Pseudomonas* spp., *Acinetobacter* spp.

Clinical use

- Alternative to β-lactams in penicillin-allergic patients with skin and soft tissue infections.
- Staphylococcal bone and joint infections.
- Severe GAS infections, e.g. necrotizing fasciitis, toxic shock syndrome (TSS).
- Anaerobic infections, e.g. intra-abdominal sepsis, anaerobic bronchopulmonary infections.
- *P. jiroveci* pneumonia (in combination with primaquine).
- *P. falciparum* malaria (in combination with quinine).

Pharmacology

- Clindamycin is given PO or IV, or by deep IM injection.
- Well absorbed orally and widely distributed with good tissue penetration, especially bone. CSF penetration is negligible.
- Most of the drug is metabolized to products with variable antibacterial activity.
- Excreted in the bile and urine—dose modification required in severe renal and liver disease.

Toxicity and side effects

- *C. difficile* colitis—discontinue clindamycin.
- Allergic reactions—rashes, fever, erythema multiforme, anaphylaxis.
- Laboratory abnormalities—transient hepatitis, neutropenia, thrombocytopenia.

Streptogramins

Streptogramins are a group of antibiotics derived from various *Streptomyces* spp. They consist of two macrocyclic lactone peptolide components referred to as streptogramin A and streptogramin B. A number of compounds exist:

- quinupristin–dalfopristin is the only drug available in the UK and used for the treatment of resistant Gram-positive infections;
- pristinamycin (used for treatment of skin and soft tissue infections);
- virginiamycin (mainly used as an animal growth promoter);
- mikamycin.

Mode of action

Streptogramins exert their action on the second or elongation stage of protein synthesis. The two components act synergistically as follows:

- streptogramin A molecules (e.g. dalfopristin) bind to the 50S ribosomal subunit and prevent aminoacyl-tRNA from attaching to the catalytic site of the peptidyl transferase, thus inhibiting transfer of the growing peptide chain;
- streptogramin B molecules (e.g. quinupristin) prevent the peptide bond from forming, which leads to the premature release of incomplete polypeptides.

Quinupristin–dalfopristin is active against most Gram-positive organisms (except *E. faecalis*, which is intrinsically resistant).

Resistance

There are three mechanism of resistance:

- modification of the ribosomal target site (quinupristin). This results in resistance to macrolides, lincosamides, and streptogramin B (MLS_B phenotype) and is encoded by various *erm* genes (➔ see Lincosamides, pp. 51–2; see Box 2.2);
- enzymatic inactivation by acetyltransferases, encoded by *vat(A)*, *vat(B)*, *vat(C)* in staphylococci, and *vat(D)* in *E. faecium* (quinupristin and dalfopristin);
- active transport out of cells by efflux pumps, encoded by *vga(A)* and *vga(B)* genes in staphylococci (quinupristin and dalfopristin).

Clinical use

- Vancomycin-resistant *E. faecium* (not active against *E. faecalis*).
- Skin and soft tissue infection caused by MSSA or GAS.
- Serious Gram-positive infections where there is no alternative antibiotic available.

Pharmacology

- Quinupristin–dalfopristin is given IV, preferably into a central vein.
- Exhibits significant PAE: 2.8h for pneumococci, 4.7h for staphylococci, and 2.6–8.5h for enterococci.
- Wide volume of distribution, but poor CSF penetration.
- Metabolized in the liver and excreted in the faeces.

Toxicity and side effects

- Injection site reactions occur in >30%, so the drug should be given via a central vein.
- Arthralgia and myalgia are common.
- Nausea, vomiting, diarrhoea, skin rash, pruritus.
- Laboratory abnormalities—hepatitis, hyperbilirubinaemia.
- Inhibition of hepatic CYP3A4, resulting in increased levels of drugs metabolized by this enzyme.

Lipopeptides

Daptomycin, a fermentation product of *Streptomyces roseosporus*, was discovered in the 1980s. It is a 13-membered cyclic amino acid lipopeptide antibiotic with a lipophilic tail. It was approved in the UK in 2003 for the treatment of complicated skin and soft tissue infections.

Mode of action

The exact mechanism of action is unknown, although it appears to bind to the cell membrane of Gram-positive bacteria in a calcium-dependent manner, disrupting the cell membrane potential. Daptomycin is active against Gram-positive organisms, e.g. staphylococci and streptococci, including those that are glycopeptide-resistant.

Resistance

Resistance to daptomycin is rare, but strains with reduced susceptibility have been obtained after serial passage *in vitro*.

Clinical use

Daptomycin is used for complicated skin and soft tissue infections caused by Gram-positive bacteria.

Pharmacology

Daptomycin is given by IV infusion. The area under the curve (AUC)/MIC profile and prolonged PAE enable od dosing. Daptomycin is highly protein-bound and is eliminated largely unchanged by the kidneys.

Toxicity and side effects

- Common side effects—nausea, vomiting, diarrhoea, headache, rash, injection site reactions.
- Muscle toxicity—myalgia, muscle weakness, and myositis are uncommon; rhabdomyolysis is rare. Serum creatine kinase (CK) should

be checked before starting treatment, and weekly during treatment. Stop treatment if symptoms develop.
- Interference with prothrombin time (PT)/international normalized ratio (INR) assay—clotting sample should be taken just prior to administration of daptomycin.

Oxazolidinones

Oxazolidinones are a purely synthetic class of antimicrobials with activity against staphylococcal and streptococcal species. Linezolid was introduced in 2001. It is active against Gram-positive bacteria and is used for infections that are resistant to other antibiotics (e.g. MRSA and VRE). Always involve an infection specialist when initiating therapy.

Mode of action

Oxazolidinones are protein synthesis inhibitors that are bacteriostatic against Gram-positive organisms. They bind to the 50S ribosomal subunit at its interface with the 30S ribosomal subunit, preventing formation of the 70S initiation complex.

Resistance

Despite its recent introduction, resistance to linezolid among strains of MRSA and VRE has already been reported. The mechanism appears to be mutation in the 23S RNA domain V region. It is usually associated with long durations of therapy or prior exposure to linezolid.

Clinical use

- Linezolid is approved for use in Gram-positive pneumonia and complicated skin/soft tissue infections, and serious infections due to resistant Gram-positive bacteria (e.g. MRSA, VRE, and penicillin-resistant pneumococci).
- Tedizolid is a related agent currently approved for acute Gram-positive skin and skin structure infections only.

Pharmacology

Linezolid may be given PO (100% bioavailability) or IV. Linezolid is widely distributed, with good tissue and CSF penetration. It is metabolized by oxidation in the liver and excreted in the urine (85%) or faeces. No dose adjustment is required for renal or hepatic disease. It is given bd; tedizolid is given daily.

Toxicity and side effects

Linezolid is generally well tolerated.
- GI symptoms, e.g. nausea, vomiting, diarrhea, are common.
- Myelosuppression—thrombocytopenia, neutropenia, and pancytopenia have been reported. Commoner with prolonged therapy (>10 days) and usually reversible. Full blood count (FBC) should be monitored weekly in patients taking linezolid.

- Monoamine oxidase inhibition—linezolid is a monoamine oxidase inhibitor. Patients should be told to avoid tyramine-rich foods. Linezolid has been associated with serotonin syndrome in patients taking concomitant selective serotonin reuptake inhibitors (SSRIs).
- Optic neuropathy has been reported in patients taking >28 days' treatment. Patients should be told to report visual symptoms and referred to an ophthalmologist, if necessary.
- Lactic acidosis has been associated with prolonged treatment.

Chloramphenicol

Chloramphenicol, initially called chloromycetin®, was first isolated from *Streptomyces venezuelae* in 1947. It has a broad spectrum of activity against a wide range of bacteria, spirochaetes, rickettsiae, chlamydiae, and mycoplasmas. Soon after its introduction in 1949, reports of aplastic anaemia emerged, limiting its use. Furthermore, widespread use in the developing world has resulted in resistance, particularly in *Salmonella* typhi. Despite this, chloramphenicol remains useful for the treatment of serious infections that are resistant to other antibiotics.

Mode of action

Chloramphenicol inhibits protein synthesis by binding to the 50S subunit of the 70S ribosome at a site that prevents the attachment of tRNA—this prevents association of the amino acid with peptidyl transferase and peptide band formation. This is a bacteriostatic effect in most organisms but is bactericidal in some meningeal pathogens, e.g. *H. influenzae, S. pneumoniae*, and *N. meningitidis.*

Resistance

There are several resistance mechanisms:

- reduced permeability or uptake;
- ribosomal mutation;
- production of acetyl transferase, an enzyme that acetylates the antibiotic into an inactive form. This mechanism also confers resistance to tetracyclines (➔ see Tetracyclines, pp. 56–8) and is responsible for widespread epidemics of chloramphenicol resistance to *S.* Typhi and *Shigella dysenteriae* seen in the developing world.

Clinical use

In the developed world, chloramphenicol is rarely used (because of toxicity), but it remains a commonly used antibiotic in the developing world.

- Enteric fever due to *S.* Typhi and *S.* Paratyphi—high rates of drug resistance have been reported in India, Vietnam, and Central and South America.
- Severe infections such as meningitis, septicaemia, epiglottitis due to *H. influenzae*.
- Sometimes used in infective exacerbations of COPD.
- An alternative agent for infections in pregnancy, young children, or patients with immediate penicillin hypersensitivity.
- Eye drops/ointment are widely used for superficial eye infections.
- Ear drops are used for bacterial otitis externa.

Pharmacology

Chloramphenicol may be administered PO, IV, IM, or TOP. It has high lipid solubility and low protein binding, resulting in a wide volume of distribution in body fluids and tissues. CSF and ocular penetration is good. Chloramphenicol is metabolized in the liver by glucuronidation and excreted in the bile. Only 5–10% is excreted in the urine.

Toxicity and side effects

- Bone marrow suppression is common, dose-related, and reversible. It is a direct pharmacological effect of the antibiotic, resulting from inhibition of mitochondrial protein synthesis. Manifestations include anaemia, reticulocytosis, leucopenia, and thrombocytopenia. Monitor FBC twice weekly during treatment.
- Aplastic anaemia is a rare, idiosyncratic, and often fatal complication, which may occur during or after completion of therapy. It occurs in 1 in 25 000–40 000 patients. The pathogenesis of this condition is incompletely understood. Monitor FBC twice weekly during treatment, and discontinue the drug if the white cell count (WCC) falls below 2.5×10^9/L.
- There are also reports of haemolytic anaemia in patients with G6PD deficiency and childhood leukaemia after chloramphenicol therapy.
- Grey baby syndrome—high doses in neonates may result in grey baby syndrome (abdominal distension, vomiting, cyanosis, circulatory collapse) due to inability to metabolize and excrete the drug. If the drug is required in neonates, the dose should be reduced and drug levels monitored.
- Other side effects—rash, fever, Jarisch–Herxheimer reactions, GI symptoms, glossitis, stomatitis, optic neuritis, bleeding disorders, acute intermittent porphyria, interference with development of immunity after immunization.

Tetracyclines

Tetracyclines are a group of broad-spectrum bacteriostatic antibiotics active against Gram-positive, Gram-negative, and intracellular organisms, e.g. *Chlamydia*, mycoplasmas, rickettsiae, and protozoan parasites. The first tetracycline chlortetracycline was isolated from *Streptomyces aureofaciens*, a soil organism. Since then, a number of other tetracyclines have been developed. Tetracyclines differ in their pharmacological properties, rather than their spectrum of cover, although minocycline has a slightly broader spectrum.

Classification

- First generation—tetracycline, chlortetracycline, oxytetracycline, demeclocycline, lymecycline, and metacycline.
- Second generation—doxycycline and minocycline.
- Third generation (glycylcyclines)—tigecycline.

Mode of action

- Tetracyclines inhibit bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit. This blocks binding of aminoacyl-tRNA to the ribosomal 'A' site, preventing the addition of new amino acids. As their binding is reversible, these agents are mainly bacteriostatic.
- Tetracyclines also inhibit mitochondrial protein synthesis by binding to 70S ribosomal subunits in mitochondria in eukaryotic parasites. The mechanism of their antiprotozoal activity is unknown.

Resistance

The widespread use of tetracyclines has been accompanied by increasing drug resistance. This is mediated by acquisition of genes on MGEs (➔ see Molecular genetics of resistance, pp. 11–2). Many tetracycline resistance genes have been identified; most belong to the *tet* family, and some belong to the *otr* family. These genes confer resistance by the following mechanisms:

- efflux pumps—these membrane-associated proteins pump tetracyclines out of the cell. They confer resistance to first-generation tetracyclines;
- ribosomal protection proteins are cytoplasmic proteins that release tetracyclines from their binding site by guanosine diphosphate (GDP)-dependent mechanisms. They protect the ribosome from first- and second-generation tetracyclines;
- enzymatic inactivation—this mechanism is seen in *B. fragilis* where the *tet(X)* gene codes for a protein that modifies tetracyclines in the presence of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and oxygen.

Clinical use

- Chlamydial infections—trachoma, psittacosis, salpingitis, urethritis, lymphogranuloma venereum (LGV).
- Rickettsial infections.
- Q fever.
- Brucellosis (doxycycline with either streptomycin or rifampicin).
- Lyme disease (*B. burgdorferi*).
- *Mycoplasma* spp. infections.
- Infective exacerbations of COPD (due to their activity against *H. influenzae*).
- Also used in acne, destructive (refractory) periodontal diseases, sinusitis, chronic prostatitis, pelvic inflammatory disease (PID), melioidosis.

Pharmacology

- Tetracyclines are usually given PO. Absorption of tetracycline and oxytetracycline is reduced by milk, antacids, and some salts. Doxycycline and minocycline are highly bioavailable.
- They are sometimes divided into three groups on the basis of their half-lives: short-acting (tetracycline, oxytetracycline), intermediate-acting (demeclocycline), and long-acting (doxycycline, minocycline).
- Tetracyclines are widely distributed and show good tissue penetration.
- Tetracycline is eliminated in the urine. Minocycline is metabolized in the liver. Doxycycline is mainly eliminated in the faeces.

Toxicity and side effects

- Nausea, vomiting, diarrhoea, dysphagia, and oesophageal irritation are common.
- Photosensitivity reactions are common and appear to be toxic, rather than allergic.
- Prolonged minocycline administration can cause skin, nail, and scleral pigmentation.
- Deposition occurs in growing bones and teeth, so tetracyclines should not be given to children <12 years or pregnant/breastfeeding women.
- Hepatotoxicity due to fatty change may be fatal.
- Tetracyclines exacerbate renal impairment. All tetracyclines (except minocycline and doxycycline) should be avoided in renal failure. Demeclocycline causes nephrogenic diabetes insipidus and is used as a treatment for inappropriate antidiuretic hormone (ADH) secretion.
- Vertigo is unique to minocycline.
- Benign intracranial hypertension has been described with all tetracyclines.
- Superinfection—mucocutaneous candidiasis is common. *C. difficile* colitis may occur.
- Allergic reactions (rashes, urticaria, anaphylaxis) are uncommon.

Tigecycline

- A glycylcycline antibiotic, structurally related to tetracyclines.
- Active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against MRSA and VRE, but not against *P. aeruginosa* and *Proteus* spp.
- Reserved for the treatment of complicated skin and soft tissue infections, and complicated abdominal infections caused by multidrug-resistant (MDR) organisms. The UK MHRA and US FDA advise use only if it is known or suspected that other antibiotics are unsuitable—pooled analysis of phase 3 and 4 trials suggested higher death rates in patients receiving tigecycline compared to those receiving comparator drugs.
- Side effects are similar to those of tetracyclines.

Sulfonamides

Prontosil was discovered in 1932, the result of 5 years of testing dyes for antimicrobial activity. It exerted its antibacterial effect through the release of sulfanilamide, an analogue of PABA. PABA is essential for bacterial folate synthesis (see Fig. 2.3). Although many sulfonamide drugs were developed, relatively few are in clinical use today, mainly because of their toxicity and increasing drug resistance. Those currently available in the UK include sulfamethoxazole, sulfadiazine, sulfadoxine, sulfasalazine, mafenide acetate, and sulfacetamide sodium.

Classification

The sulfonamides can be classified as follows:

- short-/medium-acting sulfonamides, e.g. sulfamethoxazole, sulfadiazine;
- long-acting sulfonamides, e.g. sulfadoxine;

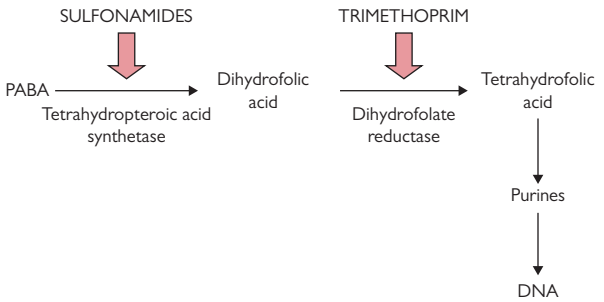

Fig. 2.3 Action of sulfonamides and trimethoprim on the bacterial folate synthesis pathway.

- sulfonamides limited to the GI tract, e.g. sulfasalazine;
- topical sulfonamides, e.g. silver sulfadiazine, mafenide acetate, sulfacetamide sodium.

Mode of action

Sulfonamides inhibit bacterial growth by competitive inhibition of the incorporation of PABA into tetrahydropteroic acid by the enzyme tetrahydropteroic acid synthetase. They are bacteriostatic and slow to act—several generations of bacterial growth are required to deplete the folate pool. They are active against a broad spectrum of Gram-positive and Gram-negative bacteria, *Actinomyces, Chlamydia, Plasmodium*, and *Toxoplasma* spp. Activity against enterococci (which are auxotrophic for folic acid), *Pseudomonas* spp. (possess drug efflux pumps), and anaerobes is poor.

Resistance

Resistance to sulfonamides is widespread and increasingly common; cross-resistance between different sulfonamides occurs. Resistance may be due to:

- chromosomal mutations that result in overproduction of PABA (e.g. *S. aureus, N. gonorrhoeae*) or alterations in dihydropteroate synthetase resulting in reduced affinity for sulfonamides (e.g. *E. coli*);
- plasmids that carry genes coding for the production of drug-resistant enzymes or decreased bacterial permeability.

Plasmid-mediated sulfonamide resistance is common in *Enterobacteriaceae* and has increased greatly in recent years, often in conjunction with trimethoprim resistance.

Clinical use

They have only a limited role as single-agent antimicrobials but are still found in combination products with trimethoprim, pyrimethamine, etc. Sulfasalazine is used for its anti-inflammatory properties (e.g. ulcerative colitis, rheumatoid arthritis)—which are probably a result of its breakdown product 5-aminosalicylic acid.

- Sulfadiazine is used in combination with pyrimethamine (➔ see Antiprotozoal drugs, pp. 119–24) for toxoplasmosis (unlicensed).
- Sulfadoxine is used in combination with pyrimethamine for treatment of falciparum malaria (➔ see Antimalarials, pp. 112–13).
- Silver sulfadiazine is used TOP to prevent/treat burn infections. Its activity is likely to owe much to the silver component.
- Sulfacetamide is used TOP in eye drops.

Pharmacology

- Usually administered PO. Sulfadiazine and sulfisoxazole are available as IV or subcutaneous (s/c) preparations.
- Oral sulfonamides are rapidly absorbed. Topical sulfonamides are also absorbed and may be detectable in blood.
- Widely distributed, with high concentrations in body fluids, including CSF.
- Metabolized in the liver and excreted in the urine. Dose modification is required in renal impairment.

Toxicity and side effects

Around 3% of people experience some form of side effect, much higher in patients with HIV. Hypersensitivity reactions are usually a class effect.

- General—nausea, vomiting, diarrhoea, rash, fever, headache, depression, jaundice, hepatic necrosis, drug-induced lupus, serum sickness-like syndrome.
- Haematological—acute haemolytic anaemia, aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia.
- Hypersensitivity reactions—drug eruption, vasculitis, erythema nodosum, erythema multiforme, Stevens–Johnson syndrome, anaphylaxis.
- Neonatal kernicterus if given in the last month of pregnancy.

Trimethoprim

Trimethoprim is a diaminopyrimidine. The other members of this class are pyrimethamine (an antiprotozoal), cycloguanil (a product of proguanil; ➔ see Antimalarials, pp. 112–13), and flucytosine (an antifungal). Trimethoprim has a fairly broad spectrum of activity against many Gram-positive bacteria and most Gram-negative rods, except *P. aeruginosa* and *Bacteroides* spp.

Mode of action

Trimethoprim inhibits the bacterial enzyme dihydrofolate reductase (DHFR), preventing the conversion of dihydrofolate to the active form of the vitamin tetrahydrofolate (➔ see Sulfonamides, pp. 58–60; see Fig. 2.3). It works on the pathway at a later point than the sulfonamides, and their combination is synergistic. It is bactericidal or bacteriostatic, depending on the organism and drug concentration.

Resistance

Resistance is common in *Enterobacteriaceae*. May be caused by:

- chromosomal mutations in the gene for DHFR (or its promoter), resulting in overproduction or modification of the target enzyme;

- plasmid-encoded resistance, e.g. *dfr* genes in *Enterobacteriaceae*, producing an additional trimethoprim-resistant DHFR enzyme;
- change in cell permeability/efflux pumps;
- alterations in metabolic pathway.

More than one mechanism can occur in the same cell, resulting in higher resistance levels.

Clinical use

- UTIs—treatment and prophylaxis.
- Treatment of prostatitis and epididymo-orchitis.
- Option for oral MRSA treatment (in combination with rifampicin or fusidic acid).

Pharmacology

- Trimethoprim is given PO and is rapidly absorbed from the gut.
- Widely distributed in tissues and body fluids, including CSF. High concentrations are achieved in the kidney, lung, sputum, and prostatic fluid.
- Sixty to 80% is excreted in the urine within 24h, the remainder excreted as urinary metabolites or in the bile.
- Synergy with sulfamethoxazole, polymyxins, and aminoglycosides.

Toxicity and side effects

- Avoid in pregnancy, especially first trimester (antifolate).
- Contraindicated in blood dyscrasias.
- Side effects are similar to those of co-trimoxazole, but less severe and less frequent with trimethoprim alone.
- Other side effects include GI disturbance, pruritus, rashes, and hyperkalaemia.
- Known to decrease the tubular secretion of creatinine which can lead to rises in serum creatinine that do not reflect a true fall in the GFR.

Co-trimoxazole

Co-trimoxazole is a synergistic combination of trimethoprim and sulfamethoxazole, in the ratio of 1:5.

Mode of action

Sequential inhibition of two enzymes (tetrahydropteroic acid synthetase and dihydrofolate reductase) in the bacterial folate synthesis pathway (➔ see Sulfonamides, pp. 58–60).

Resistance

Resistance may be due to a variety of mechanisms (for details, ➔ see Sulfonamides, pp. 58–60; ➔ Trimethoprim, pp. 60–1). Increasing drug resistance rates have been seen in *S. aureus*, many *Enterobacteriaceae*, and *Pneumocystis jiroveci*.