THE ESSENTIAL MEDICAL GUIDE FOR THE TROPICS
- DON'T LEAVE HOME WITHOUT IT!

OXFORD HANDBOOK OF TROPICAL MEDICINE

EDITED BY Robert Davidson | Andrew Ensue
Anna Seale | Lucille Blumbore

CCTipnchcnsivicly revised throughout, include up-to-daco information on viruses such as COVID-f?, HIV, arboviruses, and Ebola

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Incorporates updated guidelines Include latest WHO guidelines on HIV, TB and rabies

OXFORD HANDBOOK OF

Tropical Medicine

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Oxford Handbook of Sleep Medicine
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Handbook of Surgical Consent
Oxford Handbook of Tropical Medicine 4e
Oxford Handbook of Urology 4e

OXFORD HANDBOOK OF

Tropical Medicine

FIFTH EDITION

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Contents

Foreword

What has changed in Tropical Medicine since OHTM4e?

Epidemic infectious diseases have dominated the Tropical Medicine scene since 2014, when the last edition of OHTM was published. Outbreaks of familiar diseases have rumbled on, such as yellow fever, especially in Angola, DR Congo, Nigeria and SE Brazil; together with Chikungunya; seasonal influenza; dengue (2019–20 in the Asia Pacific region and Latin America; plague (2014–17 in Madagascar); Japanese encephalitis (India 2017); measles (e.g., in DR Congo 2019–20); and pandemic antibiotic resistance.

Ebola, Zika and COVID-19: against this background, there have been some terrible new challenges in the tropical world and globally. Ebola haemorrhagic fever, a disease discovered by Dr Jean-Jacques Muyembe in a mission hospital in Yambuku, DR Congo back in 1976, has been resurgent. A new, widespread epidemic of this highly fatal filovirus was concentrated in three West African countries in 2013–16, exacting more than 11,300 deaths, but stimulating development of some effective vaccines and treatments. Ebola recurred in DR Congo and Uganda in 2018–20 with a new outbreak in Guinea in March 2021. Zika virus caused more than 84,000 infections globally in 2015–16, mostly in Latin America and SE Asia, with an estimated 1,000 deaths, mainly among about 4,000 children born with microcephaly and other birth defects. Completely overshadowing these challenges to human health has been the global pandemic of COVID-19 which has affected 2 billion and killed 3 million people so far, leaving the debilitating symptoms of long COVID, including types 1 and 2 diabetes mellitus, in survivors.

Other challenges: the magnitude and novelty of these epidemics alone would justify a new edition of OHTM, as would the continuing problem of HIV/AIDS and tuberculosis, but, the speciality of Tropical Medicine comprises far more than infectious diseases. Non-communicable diseases continue to cause a massive burden of human suffering and deserve the attention devoted to them in OHTM5e. It is reassuring to see strong coverage of important topics, such as inherited, endocrine, nutritional and psychiatric diseases, trauma and obstetrics.

Publication of this new edition should provoke both celebration and reflection

Celebration: we celebrate the presence of OHTM, discovered on otherwise-empty bookshelves in district hospitals from Kenya's Swahili Coast to Karnataka, and from Australia's Northern Territory to PNG's Marshall Lagoon; and in the otherwise-empty pockets of health assistants, dispensers, nurses, paramedics, community health worker, and doctors, especially in rural areas of LMICs.

Reflection: what is the future of a hard copy book, whose average gestation period is 9 months from proof to printing, in the face of dynamic changes in acquisition of new knowledge essential for the optimal treatment of disease? This problem is exemplified by the surge in important new knowledge about all aspects of SARS CoV-2 virus variants. The answer would seem to be electronic publication with continual updating. However, despite the increasing reach of the world wide web, and proliferation and penetration of mobile phone connectivity, this remains impossible or inconvenient for many medical staff in search of immediate up-to-date clinical guidance. Using modern technology, might medical publishers speed up this process and deliver hard copy in weeks or a few months, as has been achieved for other non-fictional hot topics?

Editors and contributors

OTM4's editorial team of Andrew Brent, Anna Seale, and Robert Davidson is strengthened by the addition of Lucille Blumberg from the National Institute for Communicable Diseases Johannesburg, South Africa. There are some 59 listed contributors to the new edition, 30 of whom, to the editors' great credit, are new (it's far less effort to get existing authors to update, than to identify and recruit newcomers!). Although 34 of the current contributors are based in Western countries, most have evident overseas links, while 21 authors write from African countries (11 from South Africa, reflecting the footprints of two of the editors), and 4 from Asia. All have instilled valuable experiences and insights. However, in OHTM, authorship of and responsibility for a chapter must acknowledge a lineage of writers who have enhanced and updated that chapter over the 5 editions since Michael Eddleston and Stephen Pierini chipped OHTM1ed out of the bedrock.

Learning Tropical Medicine

The best way to discover Tropical Medicine and to understand its appeal and rewards is not by reading books, however good they may be, but by living and working in a tropical country, learning from your patients and experienced local doctors, and following up investigations to confirm the diagnosis. However, there are many important facts; clinical features, complex life-cycles, drug doses, vaccine regimens, and so on; that you may need—more than can reliably be memorised. Searching OHTM can reveal this vital information immediately. That is its great strength.

Congratulations!

I applaud all those, past and present, who have been involved in the OHTM project. I congratulate them for establishing its high reputation and for securing its promise of further, future, achievements. This small book, comprising barely 540 cm^3 of printed pages, remains uniquely accessible, authoritative, affordable, attractive, and appropriate for use in 'All places that the eye of heaven visits', especially tropical countries, and anywhere travel and immigrant medicine are practised.

David A. Warrell
Oxford March 2021

Preface

The first edition (1999) of the *Oxford Handbook of Tropical Medicine* was created by Michael Eddleston and Stephen Pierini, to fill a gap between standard handbooks of clinical medicine that were unsuitable for use in resource-poor settings, and World Health Organization (WHO) guidelines, which were more appropriate, but not available in a collected format. Subsequent editions have evolved, but the vision remains to provide a practical, inexpensive handbook for clinicians working with tropical diseases, especially in low-resource settings in the tropics. Lucille Blumberg joins Andrew Brent, Anna Seale, and Robert Davidson as co-editor of the fifth edition, and a large panel of international experts have once again updated each chapter.

The concept and the content of tropical medicine are continually evolving: classical tropical diseases including malaria, tuberculosis, and HIV are all thankfully declining. In many regions, non-communicable diseases have overtaken traditional tropical infections as major public health challenges. It is impossible for a single book to cater to every continent and context all the time; nevertheless, we hope the book will continue to be a useful resource for doctors, medical assistants, nurses, and other healthcare professionals in most such setting.

We only ask that readers remain critical and selective, deciding what is relevant for their own circumstances and facilities; and that they share their comments and criticisms with the editors to further improve the book for future editions. Comments can be sent via the OUP website: http://ukcatalogue.oup.com/.

Acknowledgements

We would like to thank Professor David Warrell for writing the foreword and Michael Eddleston, without whose initial vision and determination this book would not exist. Finally, we would like to extend our sincere thanks to the many expert authors who once again gave of their time and experience in writing and updating each section of the new edition.

Royalties

All royalties from the sale of this book are being donated to the Tropical Health Education Trust (THET), and the book will be available free online to readers in the developing world via the WHO HINARI portal.

Symbols and abbreviations

➲	cross-reference
❗	warning
🖱	website
💣	controversial topic
~	approximately
1°	primary
2°	secondary
3°	tertiary
↑	increased/increasing
↓	decreased/decreasing
→	leads to
+ve	positive
–ve	negative
+/–	with or without
3TC	lamivudine
ABC	airway, breathing, circulation/coma/convulsions *or* abacavir
ABCD	airway, breathing, circulation/coma/convulsions, and dehydration
ABG	arterial blood gases
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACPA	anti-citrullinated peptide antibody
ACR	American College of Rheumatology
ACT	artemisinin combination therapy
ACTH	adrenocorticotrophic hormone
ADA	adenosine deaminase
AF	atrial fibrillation
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALA	amoebic liver abscess
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALS	advanced life support
ALT	alanine transaminase
AML	acute myeloid leukaemia
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
AP	antibiotic prophylaxis
APBA	allergic bronchopulmonary aspergillosis
APTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARI	acute respiratory infection
ART	antiretroviral therapy
ASD	atrial septal defect
AST	aspartate transaminase
ATL	adult T-cell leukaemia/lymphoma
ATN	acute tubular necrosis
ATZ	atazanavir
ATZ/r	atazanavir/ritonavir
AV	atrioventricular
AVPU	alert, voice, pain, unresponsive
AXR	abdominal X ray
AZT	zidovudine
BA	bacillary angiomatosis
BAL	bronchoalveolar lavage
BCC	basal cell carcinoma
BCG	Bacille Calmette–Guérin vaccine
BCS	Blantyre Coma Scale
bd	twice daily
BHS	beta-haemolytic streptococci
BL	Burkitt's lymphoma
BLS	basic life support
BMI	body mass index
BP	blood pressure
BSA	body surface area
BSL	biosafety level
BU	Buruli's ulcer
BV	bacterial vaginosis
BVM	bag, valve, and mask
CA	cancer
CABG	coronary artery bypass grafting
CAP	community-acquired pneumonia

CATT	card agglutination Trypanosoma test
CCF	congestive cardiac failure
CCS	Canadian Cardiovascular Society
CD	Chagas' disease
CDC	Centers for Disease Control
CDLE	chronic discoid lupus erythematosus
CHIKV	Chikungunya virus
CHW	community health worker
CKD	chronic kidney disease
CL	cutaneous leishmaniasis
CLAT	cryptococcal latex agglutination test
CLD	chronic liver disease
CLL	chronic lymphocytic leukaemia
CLO	columnar-lined oesophagus
CM	cerebral malaria
CML	chronic myeloid leukaemia
CMR	crude mortality rate
CMV	cytomegalovirus
CNS	central nervous system
CO	corneal opacity
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
Cr	creatinine
CrAg	cryptococcal antigen test
CrCl	creatinine clearance
CRF	chronic renal failure
CRP	C-reactive protein
CRT	capillary refill time
CS	caesarean section
CSF	cerebrospinal fluid
CT	computed tomography
CVS	cardiovascular system
CXR	chest X-ray
D&V	diarrhoea and vomiting
d4T	stavudine
DC	direct current
DCL	disseminated cutaneous leishmaniasis
DDAVP	desmopressin
ddI	didanosine
DDT	dichlorodiphenyltrichloroethane
DEC	diethylcarbamazine
DEET	diethyltoluamide
DENV	dengue virus
DF	dengue fever
DHF	dengue haemorrhagic fever
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DILI	drug-induced liver injury
DILS	diffuse inflammatory lymphocytosis syndrome
DIP	distal interphalangeal
DKA	diabetic keto-acidosis
DM	diabetes mellitus
DMARD	disease-modifying antirheumatic drug
DMSA	dimercaptosuccinic acid (in radionuclide scan)
DOT	directly observed therapy
DOTS	directly observed therapy, short-course
DPL	diagnostic peritoneal lavage
DRC	Democratic Republic of Congo
DRV	darunavir
DSS	dengue shock syndrome
dT	combination tetanus toxoid and low-dose diphtheria toxoid vaccine for use in individuals >7yrs
DT	combination diphtheria toxoid and tetanus toxoid vaccine for use in children <7yrs
DTaP	combination diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine
DTC	diagnostic testing and counselling
DTG	dolutegravir
DTP	combination diphtheria toxoid, tetanus toxoid, and pertussis vaccine
DU	duodenal ulcer
DVT	deep venous thrombosis
DXM	dexamethasone
EAEC	enteroaggregative *Escherichia coli*
EBV	Epstein–Barr virus
ECF	extracellular fluid
ECG	electrocardiogram

ECV	extracellular volume
EEG	electroencephalogram
EEV	equine encephalitis virus
EFZ	efavirenz
EHEC	enterohaemorrhagic *Escherichia coli*
EIA	enzyme immunoassay
EIEC	enteroinvasive *Escherichia coli*
ELISA	enzyme-linked immunosorbent assay
EMB	endomyocardial biopsy
EMS	electrolyte/mineral solution
ENL	erythema nodosum leprosum
ENT	ear, nose, and throat
EPEC	enteropathogenic *Escherichia coli*
EPI	Expanded Programme on Immunization
ERCP	endoscopic retrograde cholangiopancreatography
ES	encephalopathic syndrome
ESBL	extended-spectrum beta-lactamase
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ETAT	Emergency Triage Assessment and Treatment
ETEC	enterotoxigenic *Escherichia coli*
ETF	early treatment failure
ETR	etravirine
EULAR	European League Against Rheumatism
EVD	Ebola virus disease
FAR	fever, arthralgia, and rash
FB	foreign body
FBC	full blood count
FDC	fixed-drug combination
FFP	fresh frozen plasma
FHx	family history
FNAC	fine needle aspirate cytology
FPV	fosamprenavir
FSGS	focal segmental glomerulosclerosis
FTC	emtricitabine
G6PD	glucose 6-phosphate dehydrogenase
GAM	global acute malnutrition
GAVI	Global Alliance for Vaccines and Immunisation
GBM	glomerular basement membrane
GBS	Guillain–Barré syndrome
GCS	Glasgow Coma Scale
GFD	general food distribution
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GISA	glycopeptide intermediate *Staphylococcus aureus*
GKI	glucose–K^+–insulin
GN	glomerulonephritis
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
GTN	glyceryl trinitrate
GTT	glucose tolerance test
H/A	height for age
HAART	highly active antiretroviral therapy
HAI	healthcare-associated infection
HAT	human African trypanosomiasis
HAV	hepatitis A virus
Hb	haemoglobin
HbA1c	glycated haemoglobin
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCT	haematocrit
HCV	hepatitis C virus
HCW	healthcare worker
HD	haemodialysis
HDN	haemorrhagic disease of the newborn
HDV	hepatitis D virus
HELLP	haemolysis, elevated liver enzymes, low platelets
HepB	hepatitis B vaccine
HF	haemorrhagic fever
HFNO	high flow nasal oxygen
HHV	human herpesvirus
Hib	*Haemophilus influenzae* type B
HIE	hypoxic-ischaemic encephalopathy
HIV	human immunodeficiency virus
HIV–ve	HIV negative/uninfected
HIV+ve	HIV positive/infected
HIVAN	HIV-associated nephropathy

HL	Hodgkin's lymphoma
HLA	human leucocyte antigen
HMS	hyperreactive malarial splenomegaly
HONK	hyperglycaemic hyperosmolar non-ketotic coma
HPLC	high performance liquid chromatography
HPV	human papillomavirus
HRS	hepatorenal syndrome
HSP	Henoch–Schönlein purpura
HSV	herpes simplex virus
HT	hypertension
HTLV	human T-lymphotropic virus
HUS	haemolytic uraemic syndrome
IBD	inflammatory bowel disease
ICP	intracranial pressure
ICU	intensive care unit
ID	intellectual disability
IDV	indinavir
IE	infective endocarditis
Ig	immunoglobulin
IGRA	interferon gamma release assay
IHD	ischaemic heart disease
ILD	interstitial lung disease
IM	intramuscular
IMCI	integrated management of childhood illness
INH	isoniazid
INR	international normalized ratio
IOP	intraocular pressure
IPC	infection prevention and control
IPT	intermittent preventive treatment
IPV	injected polio vaccine (Salk vaccine)
IRIS	immune reconstitution inflammatory syndrome
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine contraceptive device
IUGR	intrauterine growth retardation
IV	intravenous
IVIg	intravenous immunoglobulin
IVU	intravenous urogram
JE	Japanese encephalitis
JEV	Japanese encephalitis virus
JVP	jugular venous pressure
K	potassium
KMC	kangaroo mother care
KPC	*Klebsiella pneumoniae* carbapenemase
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma-associated herpes virus
LAM	lipoarabinomannan
LBRF	louse-borne relapsing fever
LBW	low birth weight
LDH	lactate dehydrogenase
LF	lymphatic filariasis
LFT	liver function test
LGV	lymphogranuloma venereum
LL	lepromatous
LMICs	low- and middle-income countries
LMN	lower motor neurone
LN	lymph node
LOC	loss of consciousness
LP	lumbar puncture
LPF	late parasitological failure
LPV	lopinavir
LPV/r	lopinavir/ritonavir
LRTI	lower respiratory tract infection
LT	heat-labile enterotoxin
LTB	laryngotracheobronchitis
LTBI	latent tuberculosis infection
LUQ	left upper quadrant
LV	left ventricle/ventricular
LVF	left ventricular failure
MAC	*Mycobacterium avium* complex
MALT	mucosa-associated lymphoid tissue
MAM	moderate acute malnutrition
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCL	mucocutaneous leishmaniasis
MCP	metacarpophalangeal
MCTD	mixed connective tissue disease
MCV	mean corpuscular volume
MDR	multidrug resistant
MHC	major histocompatibility complex
MI	myocardial infarction

MM	multiple myeloma
MMR	combination measles, mumps, and rubella vaccine
MMRV	combination measles, mumps, and rubella, and varicella
MR	combination measles and rubella vaccine *or* mitral regurgitation
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mitral stenosis
MSM	men who have sex with men
MSSA	methicillin sensitive *Staphylococcus aureus*
MSU	mid-stream urine
MTB	*Mycobacterium tuberculosis*
MTCT	mother to child transmission
MTP	metatarsophalangeal
MUAC	mid-upper arm circumference
MV	mitral valve
MVA	motor vehicle accident
N&V	nausea and vomiting
Na	sodium
NAAT	nucleic acid amplification test
NAT	nucleic acid test
NE	neonatal encephalopathy
NG	nasogastric
NGO	non-governmental organization
NGT	nasogastric tube
NHL	non-Hodgkin's lymphoma
NIV	non-invasive ventilation
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPH	neutral protamine Hagedorn
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NTS	non-typhoidal *Salmonella*
NVP	nevirapine
OA	osteoarthritis
od	once daily
OI	opportunistic infection
OPD	outpatient department
OPSI	overwhelming post-splenectomy infection
OPV	oral polio vaccine (Sabin vaccine)
ORS	oral rehydration solution
ORT	oral rehydration therapy
OTP	outpatient therapeutic nutrition programme
$PaCO_2$	arterial partial pressure of carbon dioxide
PAIR	percutaneous aspiration–injection–re-aspiration
PAM	primary amoebic meningoencephalitis
PAN	polyarteritis nodosa
PaO_2	arterial partial pressure of oxygen
PAS	periodic acid–Schiff
PBC	primary biliary cirrhosis
PCI	percutaneous coronary intervention
PCK	polycystic kidneys
PCNSL	primary central nervous system lymphoma
PCP	*Pneumocystis jirovecii* (formerly *carinii*) pneumonia, *Pneumocystis* pneumonia
PCR	polymerase chain reaction
PCV	packed cell volume *or* pneumococcal conjugate vaccine
PD	peritoneal dialysis
PE	pulmonary embolism
PEFR	peak expiratory flow rate
PEL	primary effusion lymphoma
PEP	post-exposure prophylaxis
PF	pemphigus foliaceous
PFT	pulmonary function test
PHT	portal hypertension
PI	protease inhibitor
PID	pelvic inflammatory disease
PIM	post-infective malabsorption
PIP	proximal interphalangeal
PJP	*Pneumocystis jirovecii* pneumonia
PKDL	post-kalar dermal leishmaniasis
PLHIV	people living with HIV
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother to child transmission (of HIV)
po	'per os' (oral)
POCs	products of conception
PPE	personal protective equipment
PPI	proton pump inhibitor
PPV	pneumococcal polysaccharide vaccine

pr	per rectum
PR	pulse rate
PrEP	pre-exposure prophylaxis
pSBI	possible serious bacterial infection
PT	prothrombin time
PTB	pulmonary tuberculosis
PTH	parathyroid hormone
PTSD	post-traumatic stress disorder
PUD	peptic ulcer disease
PV	per vagina
PVD	peripheral vascular disease
qds	four times a day
R	rifampicin
RA	right atrium *or* rheumatoid arthritis
RAL	raltegravir
RAST	radioallergosorbent test
RBBB	right bundle branch block
RBC	red blood cell
RCT	randomized controlled trial
RDA	recommended daily allowance
RDT	rapid diagnostic test
REM	rapid eye movement
RF	rheumatic fever
RhF	rheumatoid factor
RIF	rifampicin
RIG	rabies immunoglobulin
RNA	ribonucleic acid
Rota	rotavirus vaccines
RPR	rapid plasma reagin
RR	respiratory rate *or* relative risk
RSV	respiratory syncytial virus
RTV	ritonavir
RUQ	right upper quadrant
RUSF	ready-to-use supplementary foods
RUTF	ready-to-use therapeutic food
RV	right ventricle/ventricular
RVF	right ventricular failure
SAFE	surgery for trichiasis, antibiotics, facial cleanliness, and environmental improvement
SAH	subarachnoid haemorrhage
SAM	severe acute malnutrition
SaO_2	oxygen saturation
SARS	severe acute respiratory syndrome
SBE	subacute bacterial endocarditis
SBP	spontaneous bacterial peritonitis
SC	subcutaneous
SCC	squamous cell carcinoma
SCLE	subacute cutaneous lupus erythematosus
SFP	supplementary feeding programme
SGA	small for gestational age
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIN	squamous intraepithelial neoplasia
SIRS	systemic inflammatory response syndrome
SJS	Stevens–Johnson syndrome
SLE	systemic lupus erythematosus
SMX	sulfamethoxazole
SOB	short of breath
SOL	space-occupying lesion
SOP	standard operating procedure
SP	sulfadoxine–pyrimethamine
SQV	saquinavir
SSI	surgical site infection
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin reuptake inhibitor
STEMI	ST-elevation myocardial infarction
STH	soil-transmitted helminth
STI	sexually transmitted infection
SVT	supraventricular tachycardia
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TBM	tuberculosis meningitis
TBRF	tick-borne relapsing fever
TCA	tricyclic antidepressant
TCBS	thiosulfate-citrate-bile salts-sucrose agar
TDF	tenofovir
tds	three times a day
TEN	toxic epidermal necrolysis
TetT	tetanus toxoid vaccine
TF	trachomatous inflammation—follicular
TFP	therapeutic feeding programme
TFT	thyroid function test

TI	trachomatous inflammation—intense
TIA	transient ischaemic attack
TIBC	total iron-binding capacity
TIPS	transjugular intrahepatic portosystemic shunting
TMP	trimethoprim
TPE	tropical pulmonary eosinophilia
TR	tricuspid regurgitation
TS	trachomatous scarring
TSH	thyroid-stimulating hormone
TSP	tropical spastic paraparesis
TST	tuberculin skin test
TT	trachomatous trichiasis
TTP	thrombotic thrombocytopenic purpura
U&E	urea & electrolytes
U5MR	under-five mortality rate
ULN	upper limit of normal
UMN	upper motor neurone
UNHCR	United Nations High Commission on Refugees
UNICEF	United Nations International Children's Emergency Fund
URTI	upper respiratory tract infection
US	ultrasound
USA	United States of America
USS	ultrasound scan
UTI	urinary tract infection
UV	ultraviolet
UVC	umbilical vein catheter
VA	visual acuity
VCT	voluntary counselling and testing
VDRL	syphilis serology (Venereal Disease Research Laboratory)
VF	ventricular fibrillation
VHF	viral haemorrhagic fever
VKDB	vitamin K deficiency bleeding
VL	viral load *or* visceral leishmaniasis
VRE	vancomycin-resistant enterococcus
VSD	ventriculoseptal defect
VSW	visible severe wasting
VT	ventricular tachycardia
VUR	vesicoureteric reflux
VVM	vaccine vial monitor
VZV	varicella zoster virus
W/A	weight for age
W/H	weight for height
WBC	white blood cell
WCC	white cell count
WDM	whole dried milk
WHO	World Health Organization
WNV	West Nile virus
XDR	extensively drug resistant
YF	yellow fever
Z	pyrazinamide
ZIKV	Zika virus
ZN	Ziehl–Nielsen (stain for acid-fast bacilli)

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The *Oxford Handbook of Tropical Medicine* would not be the resource it is without the generous contributions of a large number of section authors, each of whom is an international expert in their field and has given freely of their time to ensure the book is as up to date and relevant as possible. With each new edition the editors have invited new contributors to update selected sections of the book, many of whom have built on the content of previous authors. The editors would like to acknowledge the important contribution of previous authors, all of whom are listed below.

We remember with sadness Prof Bongani Mayosi of the University of Cape Town, who died tragically while this book was in preparation.

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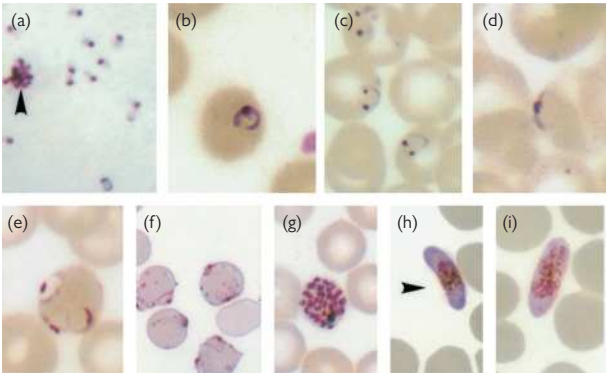


Plate 1 *Plasmodium falciparum.* (a) Thick film showing ring trophozoites + schizont (arrow); and thin films showing: ring trophozoites [(b) to (f)]—note the single and double chromatin dots, multiply infected erythrocytes, accolé form (d) and Maurer's clefts (f); schizont (g); macrogametocyte (h); and microgametocyte (i). Reproduced with permission from WHO Bench Aids for the Diagnosis of Malaria Infections, 2nd ed.

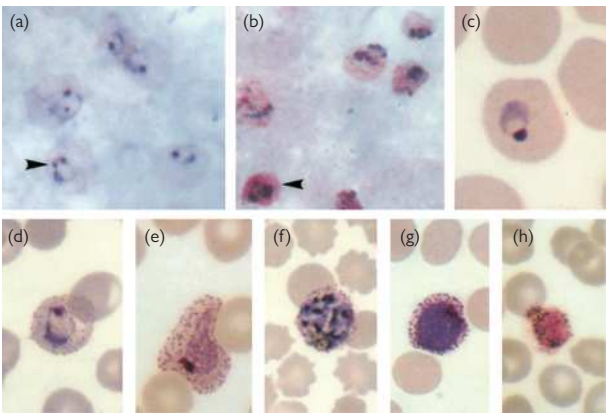


Plate 2 *Plasmodium vivax.* Thick films (a) and (b) showing ring forms; and thin films showing: ring trophozoites of varying size and shape [(c) to (e)], schizont (f), microgametocyte (g), and macrogametocyte (h). Note Schüffner's dots seen as stippling in the surface of the erythrocyte. Reproduced with permission from WHO Bench Aids for the Diagnosis of Malaria Infections, 2nd ed.

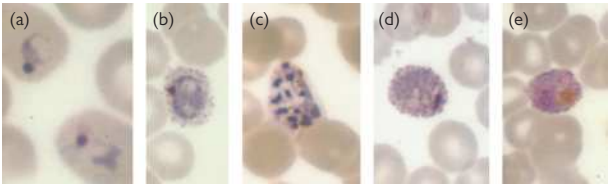


Plate 3 *Plasmodium ovale*. (a) and (b) Thin films showing trophozoites; (c) schizont; (d) microgametocyte and; (e) macrogametocyte. Reproduced with permission from WHO Bench Aids for the Diagnosis of Malaria Infections, 2nd ed.

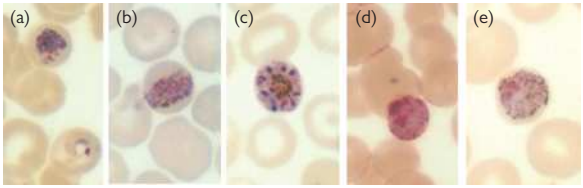


Plate 4 *Plasmodium malariae*. (a) Thin films showing trophozoites, including (b) band form; (c) schizont; (d) microgametocyte and; (e) macrogametocyte. Reproduced with permission from WHO Bench Aids for the Diagnosis of Malaria Infections, 2nd ed.

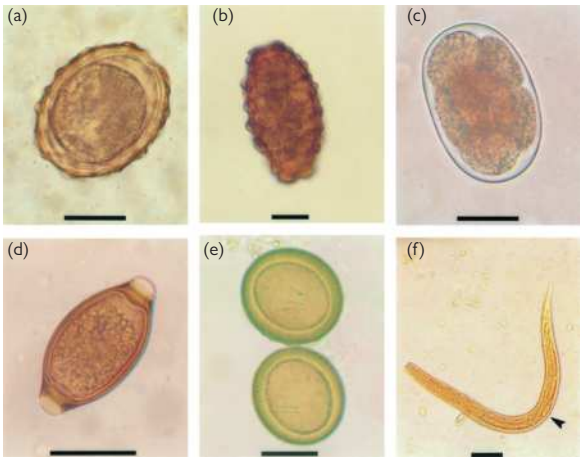


Plate 5 Faecal parasites 1. (a) Ascaris egg (fertile); (b) Ascaris egg (infertile); (c) Hookworm egg; (d) Trichuris egg; (e) Taenia eggs; (f) Rhabtidiform larva of *Strongyloides stercoralis*. [Scale: bar = 25 µm]. Reproduced with permission from WHO Bench Aids for the Diagnosis of Faecal Parasites.

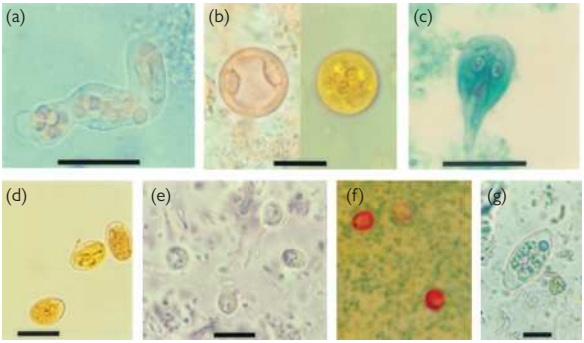


Plate 6 Faecal parasites 2. (a) *Entamoeba histolytica* trophozoite (note phagocytosed erythrocytes); (b) *E. histolytica* cysts; (c) *Giardia lamblia* trophozoite; (d) *G. lamblia* cysts; (e) *Cryptosporidium parvum* oocysts (wet prep); (f) *Cryptosporidium parvum* oocysts (Ziehl–Neelsen stain); (g) *Isospora belli* cyst. [Scale: bar = 10 μm]. Reproduced with permission from WHO Bench Aids for the Diagnosis of Faecal Parasites.

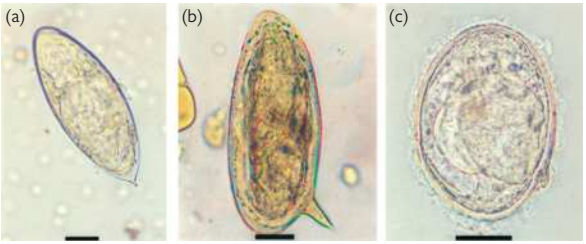


Plate 7 Schistosomiasis eggs. (a) *S. haematobium* (in urine); (b) *S. mansoni* (in stool); (c) *S. japonicum* (in stool). [Scale: bar = 25 μm]. Reproduced with permission from WHO Bench Aids for the Diagnosis of Faecal Parasites.

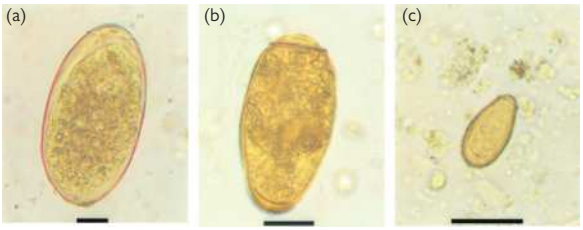


Plate 8 Other trematodes. (a) *Fasciola hepatica* egg; (b) *Paragonimus westermani* egg; (c) *Clonorchis sinensis* egg. [Scale: bar = 25 μm]. Reproduced with permission from WHO Bench Aids for the Diagnosis of Faecal Parasites.

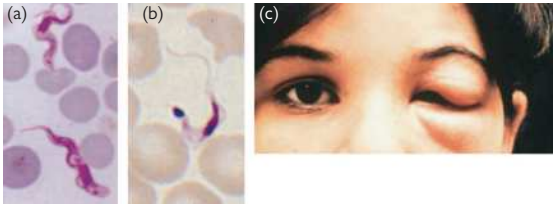


Plate 9 Trypanosomes. (a) *Trypanosoma b. rhodesiense* (Giemsa); (b) *Trypanosoma cruzi* (Leishman stain); (c) Romaña's sign (unilateral oedema and conjunctivitis at the portal of entry in acute Chagas' disease). (c) Reproduced with permission from WHO/TDR Image library © http://www.who.int/tdr/tropical_diseases/databases/imagelib.pl?imageid=9305157

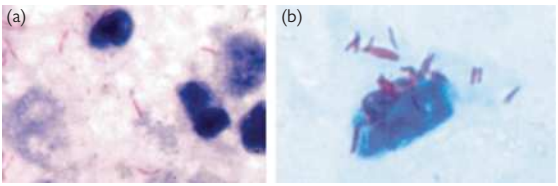


Plate 10 Mycobacteria. (a) *M. tuberculosis* in sputum smear; (b) *M. leprae* in skin smear—note acid-fast bacilli in and around macrophage (both Ziehl–Neelson stain). Oxford Handbook of Tropical Medicine 2e.

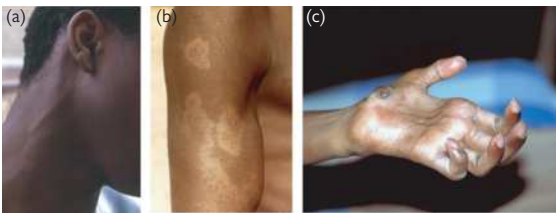


Plate 11 Leprosy. (a) Thickened greater auricular nerve; and (b) hypopigmentation in tuberculoid leprosy; (c) typical deformity and neuropathic ulcer in lepromatus leprosy. (a) Image courtesy of Robert Davidson; (b) Image courtesy of Anthony Bryceson; (c) Reproduced with permission from WHO © http://medicine.plosjournals.org/perlserv/?request=slideshow& type=figure&doi=10.1371/journal.pmed.0020341&id=41756

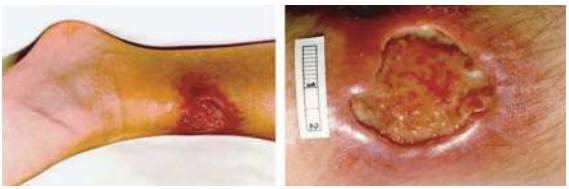


Plate 12 Buruli ulcer. Note the undermined edges of the ulcer. Reproduced with permission from PLoS (© http://medicine.plosjournals.org/perlserv?request=slideshow&type=figure&doi=10.1371/journal.pmed.0020108&id=25784)

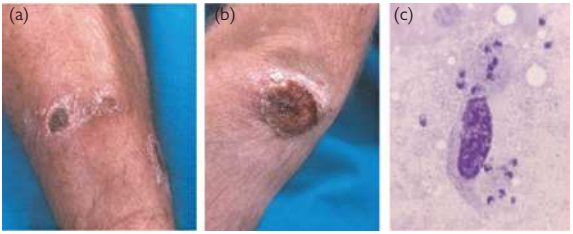


Plate 13 Leishmaniasis. (a) Leg and (b) elbow with cutaneous leishmaniasis from Belize due to *Leishmania braziliensis*; (c) *Leishmania* amastigotes in slit skin smear. Image courtesy of Rob Davidson.

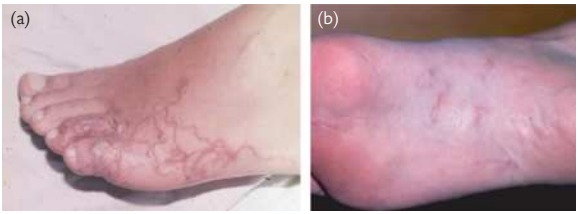


Plate 14 Cutaneous larva migrans. (a) Image courtesy of Anthony Bryceson; (b) Image courtesy of Terence Ryan.

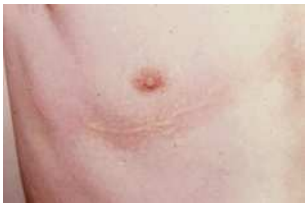


Plate 15 Larva currens. Image courtesy of Anthony Bryceson.

Plate 16 Molluscum contagiosum. Reproduced with permission from Cotell SL, Roholt NS. Images in clinical medicine. *Molluscum contagiosum in a patient with the acquired immunodeficiency syndrome*. N Engl J Med. 1998;338:888, with permission.

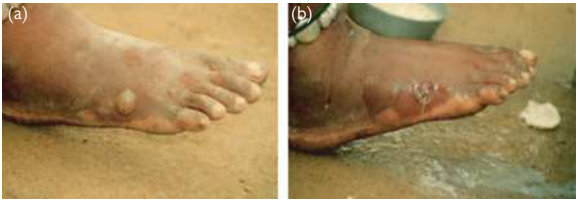


Plate 17 Dracunculiasis. The female guinea worm induces a painful blister (a), through which she protrudes (b) to lay her eggs when water is poured over the site. Reproduced with permission from CDC ℞ www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Dracunculiasis_il.htm

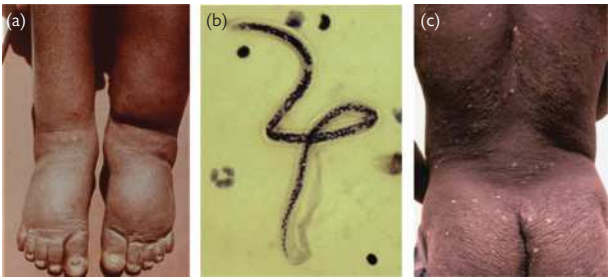


Plate 18 Filaria. (a) Lymphoedema (elephantiasis), due to (b) *Wuchereria bancrofti* (blood smear, haematoxylin); (c) onchocerciasis—chronic papular onchodermatitis. (a) and (c) Image courtesy of Anthony Bryceson. (b) Reproduced with permission from CDC ℞ http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Filariasis_il.htm

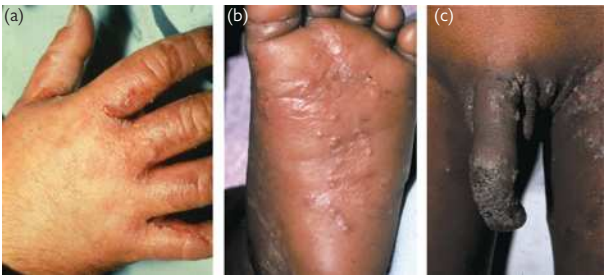


Plate 19 Scabies. (a) Hand (note predilection for web spaces), (b) foot, (c) groin. Reproduced with permission from TALC Bench Aids for Dermatology, with permission.

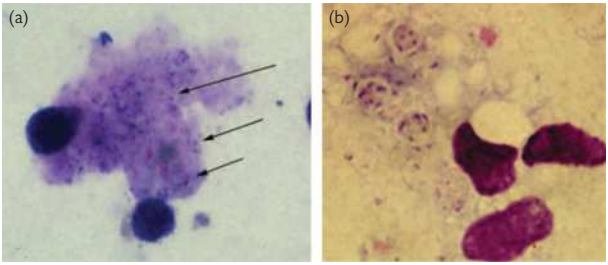


Plate 20 Pneumocystis pneumonia (PCP). (a) *Pneumocystis jirovecii* trophozoites in bronchoalveolar lavage (BAL) from patient with HIV (Giemsa). The trophozoites are small (1–5 μm), and only their nuclei, stained purple, are visible (arrows). (b) 3 *Pneumocystis jirovecii* cysts in BAL (Giemsa stain). The rounded cysts (4–7 μm) contain 6 to 8 intracystic bodies, whose nuclei are stained by Giemsa; the walls of the cysts are not stained; note the presence of several smaller, isolated trophozoites. Reproduced with permission from CDC http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Pneumocystis_il.htm

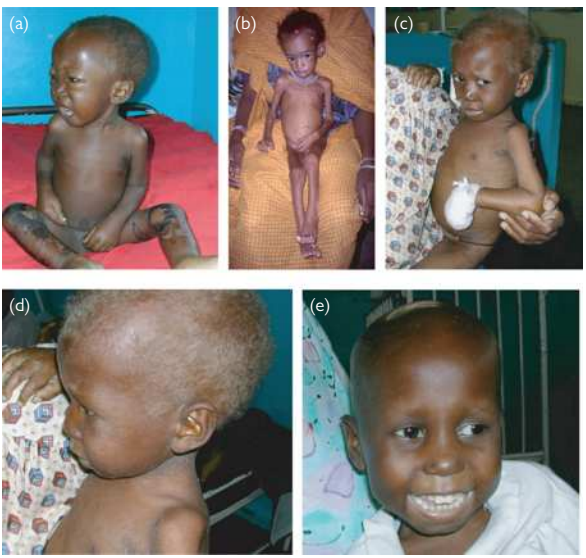


Plate 21 Malnutrition. (a) kwashiorkor—miserable affect, periorbital and limb oedema, protuberant belly, skin and hair changes; (b) marasmus—severe wasting; (c) & (d) marasmus-kwashiorkor—wasting, hair changes, and early skin changes in axilla and groin; (e) is the same child one month later after nutritional rehabilitation. (a), (c) – (e) Andrew Brent; (b) Rob Davidson.

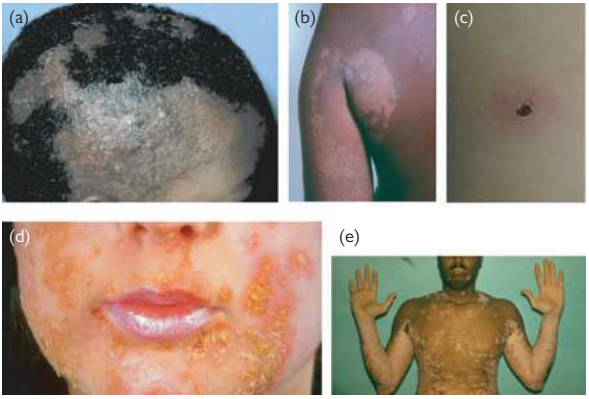


Plate 22 Miscellaneous dermatology. (a) Tinea capitis; (b) tinea corporis; (c) Rickettsial eschar (African tick bite fever); (d) impetigo; (e) vitiligo. (a) TALC Bench Aids for Dermatology; (b), (d), (e) Terence Ryan; (c) Andrew Brent.

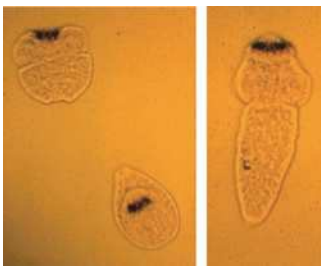


Plate 23 Hydatid sand. *Echinococcus granulosus* protoscolices in hydatid cyst fluid. Reproduced with permission from CDC http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Echinococcosis_il.htm

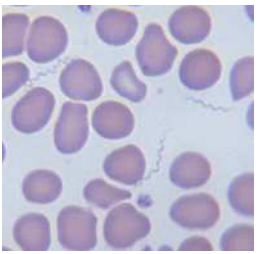


Plate 24 *Borrelia recurrentis* spirochaetes in blood film. Reproduced with permission from http://library.med.utah.edu/WebPath/COW/COW077.html

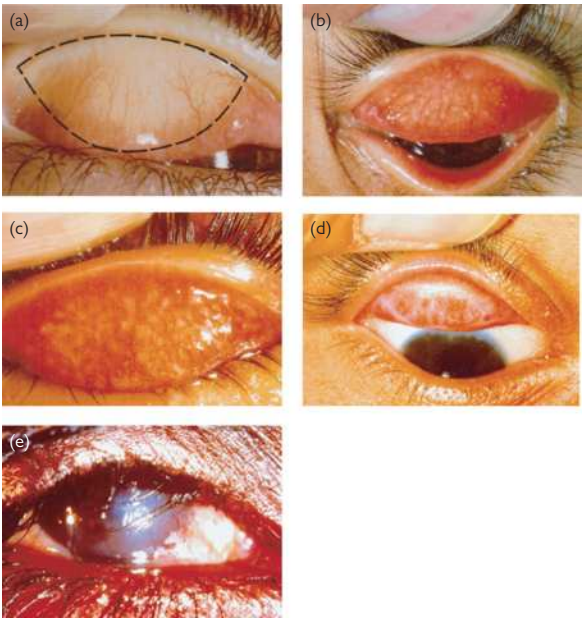


Plate 25 Trachoma. (a) Normal tarsal conjunctiva (area to be examined outlined by dotted line); (b) follicular trachomatous inflammation (>5 follicles in the upper tarsal conjunctiva); (c) intense trachomatous inflammation (inflammatory thickening partially obscures numerous follicles; (d) trachomatous scarring (white bands or sheets in the tarsal conjunctiva); (e) trachomatous trichiasis and corneal opacity (eyelashes rub on cornea which eventually clouds).

Plate 26 Saharan horned viper (*Cerastes cerastes*) specimen from Egypt. The commonest cause of venomous snake-bite throughout the Sahel region and some Middle Eastern countries. Not all specimens have the supra-ocular horns. Venom causes local swelling, blood clotting disorders, and acute kidney injury. Image courtesy of Prof David Warrell.

Plate 27 Puff adder (*Bitis arietans*) specimen from Babile, Ethiopia. The commonest cause of venomous snake-bite throughout the savannah region of Africa. Distinguished by the 'U' or 'V' markings down its back. Causes shock and severe local envenoming often leading to necrosis. Image courtesy of Prof David Warrell.

Plate 28 Common krait (*Bungarus caeruleus*) specimen from Pune, India. One of the commonest causes of fatal snake-bites throughout South Asia. Black with a white belly and paired narrow dorsal white bands. It bites people who are sleeping on the floor of their dwellings, causing severe abdominal pain and descending paralysis. Image courtesy of Prof David Warrell.

Plate 29 Bushmaster (*Lachesis muta rhombeatus*) specimen from Alagoas, Brazil. The Western hemisphere's longest venomous snake, growing up to 3.5 m in length. Its rough skin is likened to a pineapple or jack fruit. Its venom causes shock, myocardial damage, gastrointestinal symptoms, and blood clotting disorders. Image courtesy of Prof David Warrell.

Plate 30 Egyptian cobra (*Naja haje*) specimen from Watamu, Kenya: Cleopatra's 'asp'. It occurs in many colour varieties and is favoured by snake charmers throughout Africa, some of whom it has killed. Its venom causes descending paralysis. Image courtesy of Prof David Warrell.

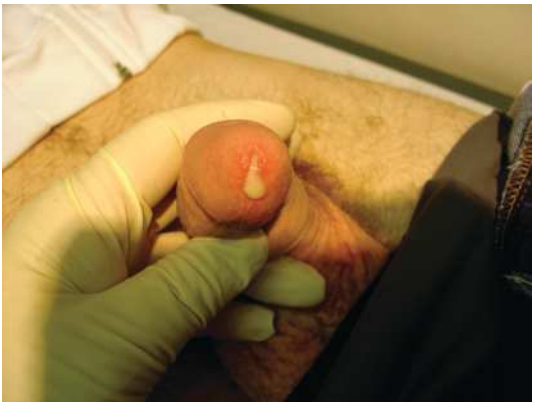


Plate 31 Gonorrhoea causing urethral discharge. Image courtesy of Melbourne Sexual Health Centre (www.mshc.org.au), Alfred Health, Melbourne, Australia, reference http://stiatlas.org/

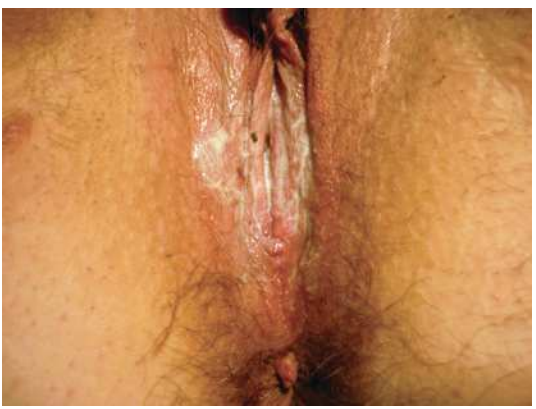


Plate 32 Vaginal discharge (BV). Image courtesy of Melbourne Sexual Health Centre (www.mshc.org.au), Alfred Health, Melbourne, Australia, reference http://stiatlas.org/

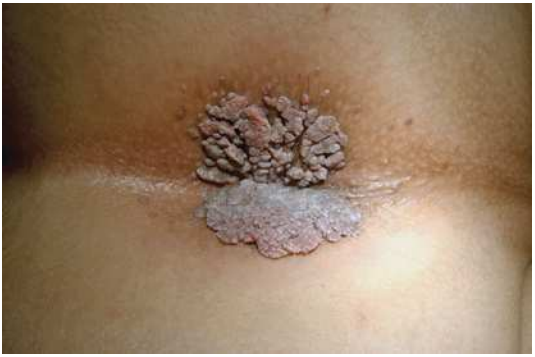


Plate 33 Genital warts. Image courtesy of Melbourne Sexual Health Centre (www.mshc.org.au), Alfred Health, Melbourne, Australia, reference http://stiatlas.org/

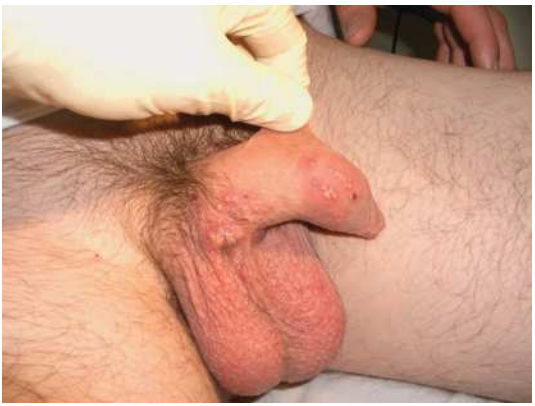


Plate 34 HSV. Image courtesy of Melbourne Sexual Health Centre (www.mshc.org.au), Alfred Health, Melbourne, Australia, reference http://stiatlas.org/

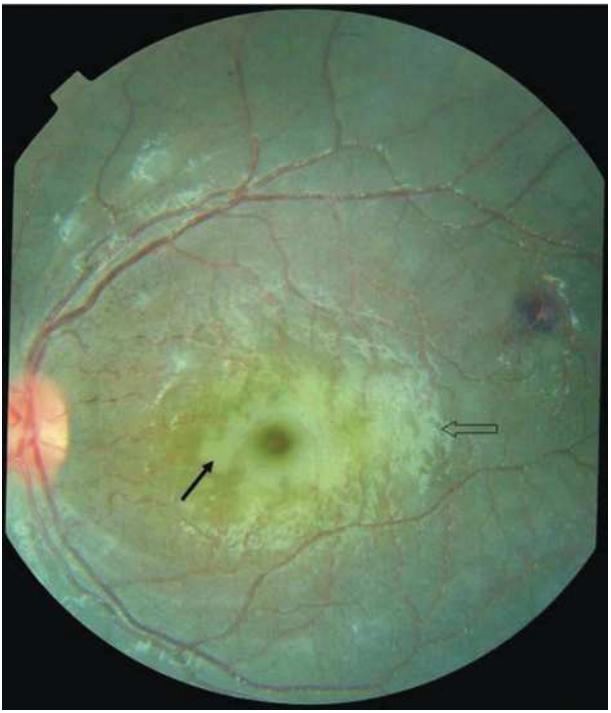


Plate 35 Severe macular whitening (solid arrow) completely surrounding the foveola of a child with cerebral malaria. Papilloedema is present as well as a white-centred haemorrhage temporal to the macula and cotton wool spots above superior temporal arcade. The open arrow indicates glare. Image courtesy of American Journal of Tropical Medicine and Hygiene.

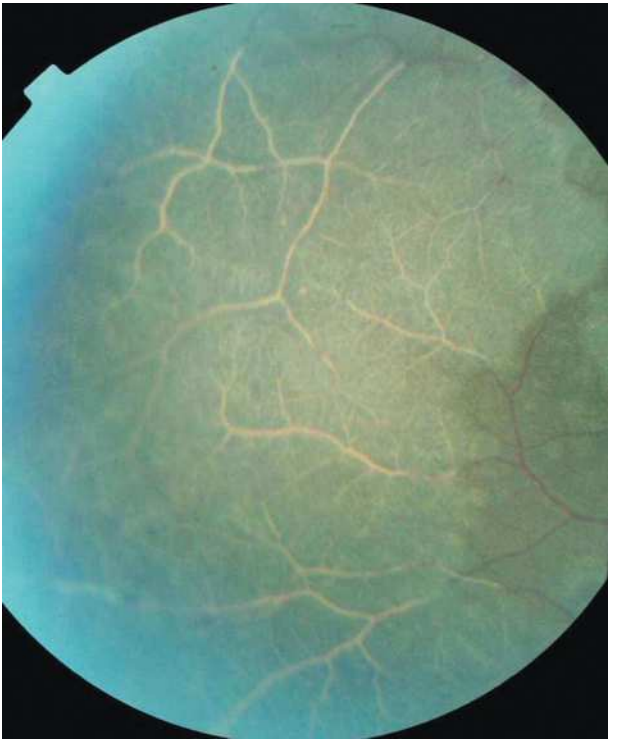


Plate 36 Cerebral malaria: white retinal vessels in an area of confluent peripheral retinal whitening. Image courtesy of American Journal of Tropical Medicine and Hygiene.

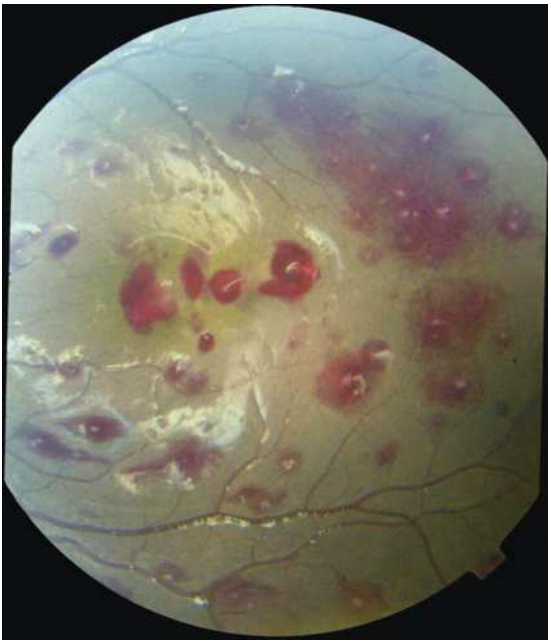


Plate 37 Large number of retinal haemorrhages in a child with cerebral malaria. Image courtesy of American Journal of Tropical Medicine and Hygiene.

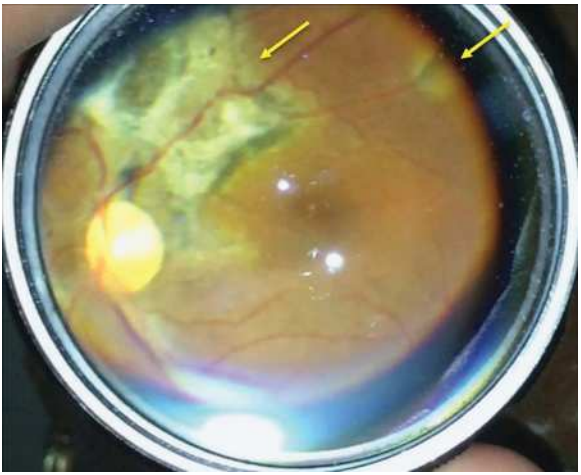


Plate 38 Retina of an Ebola survivor shows multifocal chorioretinal scarring (yellow arrows) indicative of posterior uveitis. Image courtesy of PLoS Negl Trop Dis.

Chapter 1

Management of the sick child

Elizabeth Molyneux

Bernadette O'Hare

Introduction

Of the 5.2 million deaths/yr that occur in children <5yrs, 2.4 million occur in the 1st month of life and 70% of the others are caused by acute respiratory infections, diarrhoea, measles, and malaria, +/– malnutrition. Many very sick children present with clinical features of more than one diagnosis; thus, a single diagnosis at admission may be impossible. In many low-resource settings, there is no paediatrician and sick children are managed by non-specialists.

Deaths in hospitals often occur within the first 24h, so sick children need to be identified on arrival, and appropriate treatment instituted. The Emergency Triage Assessment and Treatment (ETAT) strategy, advocated by the World Health Organization (WHO), is a rapid screening process to identify children who require immediate treatment to avert death and long-term morbidity. Treatment of sick children must never be on a 'first come, first served' basis. WHO has published guidelines for the management of common childhood illnesses (second edition 2013), available online (Box 1.1).

Box 1.1 WHO online paediatric publications

- *Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources*. Available at: https://apps.who.int/iris/handle/10665/81170
- *Emergency triage, assessment and treatment: manual for participants*. Available at: http://apps.who.int/iris/bitstream/handle/10665/43386/9241546875_eng.pdf?sequence=1 and updated guidelines: Paediatric emergency triage, assessment and treatment https://apps.who.int/iris/bitstream/handle/10665/204463/9789241510219_eng.pdf?sequence=1
  - Developed by the WHO for rapid screening of sick children to identify those with emergency, priority, or non-urgent signs (triage).
  - Children should be prioritized on presence of emergency signs, rather than on a 'first come, first served' basis.
  - All healthcare workers (HCWs) should triage and follow ABCD approach (airway, breathing, circulation/coma/convulsions, and dehydration).
  - Disease-specific treatment should be started after managing ABCD.
- *Integrated management of childhood illness (IMCI)*. Available at: https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/child-health/integrated-management-of-childhood-illness/
  - IMCI uses a syndromic approach. Combines management of individual diseases with nutrition, immunization, and maternal health. It aims to ↑ skills of HCWs.
  - 'Danger signs' are first identified. Children are then assigned defined clinical syndromes on the basis of simple questions and a basic clinical examination; >1 syndrome may be assigned.
  - The severity of each syndrome is defined and management directed: either urgent referral to 2° care, treatment and advice, or advice to the parent/caregiver for home management.
  - IMCI is targeted at HCWs in health centres and outpatient department (OPD) of small hospitals. This can be extended to incl. community health workers, shopkeepers, and pharmacists, who are often the first contact for medical advice.
  - IMCI has ↑ healthcare-seeking behaviour, rational prescribing, immunization coverage, and availability of basic equipment, and ↓ costs.
  - ↓↓ mortality should result from combining IMCI with key programmes, such as the WHO pneumonia and diarrhoea case management strategies.

Emergency triage assessment

Immediately on presentation to a health facility (i.e. *before* joining a queue), children should be rapidly triaged to identify those with:

- *Emergency signs*: require immediate treatment to prevent death (Box 1.2; ➲ Emergency management of the sick child—ABC, p. 8).
- *Priority signs*: should be assessed and treated without delay (Box 1.3).
- *Non-urgent cases* that have neither emergency nor priority signs should follow the regular queue.

Triage should be carried out at the first point of contact; this may be at the OPD, the emergency room, or paediatric ward. Children must be assessed for these signs *before* any routine procedures like registration and weighing.

Assess airway and breathing

- Look, listen, and feel for chest movement, exhaled air, and breathing sounds by placing your ear close to the child's nostrils.
- Check for respiratory distress and signs of airway obstruction (Box 1.4).
- Check the tongue and buccal mucosa for central cyanosis.
- Do not move neck if cervical injury is possible, e.g. following trauma. Use jaw-thrust manoeuvre to open the airway if needed.

Box 1.2 Emergency signs

- Obstructed noisy breathing
- Central cyanosis
- Severe respiratory distress
- Signs of shock
- ↓ level of consciousness
- Convulsion
- Severe dehydration

Box 1.3 Priority signs (3Ts 3Ps 3Rs MOB)

- Tiny (any child <2 months)
- Temperature (very hot to feel)
- Trauma
- Pain
- Pallor (severe)
- Poisoning
- Referral (urgent)
- Respiratory distress
- Restlessness
- Malnutrition (severe)
- Burns
- Oedema (bilateral pedal)

Box 1.4 Signs of severe respiratory distress

- Lower chest wall indrawing (Fig. 1.1).
- Grunting.
- Inability to speak, drink, or feed due to respiratory distress.
- Head nodding/use of accessory muscles of respiration.

Other signs of respiratory distress

- Fast breathing: ≥60 breaths/min in infants <2mths; ≥50/min in children 2–11mths; ≥40/min in children 12mths–5yrs.
- Nasal flaring.

Signs of obstructed breathing

- Inability to speak.
- Splinted chest.
- Stridor
- Weak cough
- Drooling

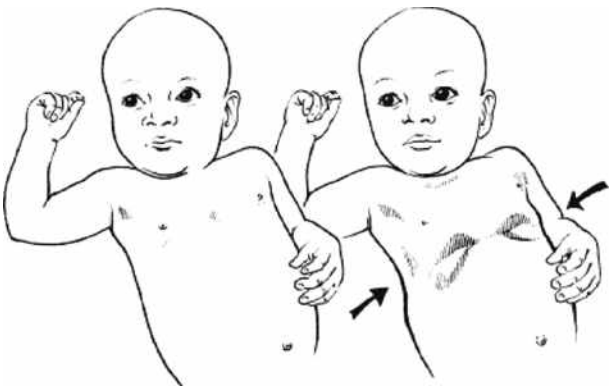


Fig. 1.1 Lower chest wall indrawing: with inspiration the lower chest wall moves in. (Note the distinction between lower chest wall *indrawing* and *intercostal recession*, in which the soft tissue between the ribs is sucked inwards on inspiration. Intercostal recession alone is not a sign of severe respiratory distress.) Controversially, the 2013 WHO guidelines for pneumonia changed lower chest indrawing from a sign of severe pneumonia to non-severe pneumonia.

Assess circulation for signs of shock

- Are the child's hands cold?
- *Assess capillary refill time (CRT)*: apply pressure to whiten nail of thumb or big toe for 5s. Release pressure and note how long it takes nail bed to refill and turn pink; CRT ≥3s is usually a sign of shock.
- *Check pulse*: if radial pulse not palpable, feel for brachial or femoral pulse in infant, or carotid pulse in older children. In hypovolaemic shock, central pulses may be weak and rapid, or absent. In septic (distributive) shock you may find warm peripheries, CRT <1s, and bounding pulse.
- *Blood pressure (BP)*: if able to measure BP you may see a wide pulse pressure, but measurement of BP is difficult in children (important to have correct cuff size), and low BP is a late clinical sign.
- WHO definition of shock is given in Box 1.5.

Assess for coma, convulsions, or other abnormal mental status

- Check for continued irritability, restlessness, lethargy, or convulsions.
- Assess level of consciousness using AVPU scale (Box 1.6) or Blantyre Coma Scale.

If diarrhoea, assess for severe dehydration

- Ask the parent if the child's eyes are unusually sunken.
- Assess skin turgor by pinching skin of abdomen halfway between umbilicus and flank. Pinch for 1s and observe how the skin returns. >2s implies marked ↓ skin turgor.
- Severe dehydration is defined as ≥2 of lethargy or unconsciousness; sunken eyes; marked loss of skin turgor; inability to drink or drinking poorly.
- Signs of severe dehydration are unreliable in children with severe malnutrition. Management should be guided by a history of diarrhoea and parental recognition of sunken eyes. See Box 1.7 for calculation of maintenance fluids.

Assess for signs of severe malnutrition

- Examine for severe muscle wasting, esp. ribs, shoulders, arms, buttocks, and thighs.
- Assess mid-upper arm circumference (MUAC): if <11.5cm (age 6mths–6yrs) or bilateral pedal oedema +/– other signs of kwashiorkor, treat as severe malnutrition.

Assess for severe anaemia

Compare the colour of the child's palm with that of the mother +/– father: if the skin is very pale or so pale that it looks white, the child has severe palmar pallor.

Assess for a major burn

See ➲ Burns, p. 809.

Assess for other priority indicators

- All infants <2mths.
- All children referred from another health facility.

Box 1.5 WHO-defined shock

Cold hands *and* CRT >3s, *and* weak, fast pulse.

Signs of hypovolaemic shock (e.g. due to dehydration)

- Temperature gradient (peripheries much colder than trunk).
- CRT >3s.
- Fast, weak pulse.

Signs of distributive shock

- Warm hands and feet: no temperature gradient.
- CRT <1s.
- Bounding pulses.
- Large pulse pressure with low diastolic BP.

Also note

- Anuria.
- Hypotension is a late sign in children.
- Altered level of consciousness.
- Acidotic (Kussmaul) breathing 2° to poor tissue perfusion.

Box 1.6 AVPU scale

The AVPU scale is a simple way of rating level of consciousness:

- **A** Alert.
- **V** Responds to verbal commands.
- **P** Responds to painful stimulus. Press down firmly on the middle fingernail with a pen, or rub your knuckles on the sternum.
- **U** Unresponsive.

Box 1.7 Calculating maintenance fluids in children

- If oral or nasogastric (NG) feeds tolerated, these are preferable to intravenous (IV) fluids.
- Daily maintenance IV fluid requirement:
  - 100mL/kg for the first 10kg.
  - 50mL/kg for the next 10kg.
  - 25mL/kg for each subsequent kg.
- E.g. a 6kg infant receives 6 × 100mL = 600mL/d, an 18kg child (10 × 100) + (8 × 50) = 1400mL/d.
- An alternative is 4mL/kg/h for the first 10kg, 2mL/kg/h for the second 10kg and 1mL/kg/h for each subsequent kg. For example, a 6kg infant receives 6 × 4mL/h = 24mL/h, an 18kg child (4 × 10) + (2 × 8) = 56mL/h.
- For neonates, see feed and fluid requirements (➲ Fluid requirements, p. 20).
- Fluid requirements ↑ in febrile children, and in hot environments.

Emergency management of the sick child—ABC

If emergency signs are present, call for help and give emergency treatment:

Airway and breathing

- Severe respiratory distress, obstructed breathing, or central cyanosis is an emergency.
- If there is a history or evidence of foreign body aspiration, manage as for a choking child (➲ Foreign body aspiration in an unconscious child, p. 9).
- Open airway using head tilt and chin lift. In infants, avoid causing obstruction by hyperextension: the 'tilt' should be to the neutral position. In older children, tilt the head to the 'sniffing' position (Fig. 1.2).
- If this fails to open the airway (or if you suspect cervical spine injury), use the jaw-thrust manoeuvre to open the airway: place the first two fingers of each hand behind each side of the child's mandible and move the jaw forward.
- Inspect the mouth and remove any visible foreign body.
- Clear secretions from oropharynx (use suction if available).
- If inadequate respiratory effort, use bag, valve, and mask (BVM) ventilation: 40–60 breaths/min in newborns, 20–30 breaths/min in infants, and 16–20 breaths/min in older children.
- Where expertise/facilities exist, perform endotracheal intubation. Attempted intubation by the inexperienced must not compromise adequate BVM ventilation.

Foreign body aspiration in a choking, conscious child or infant

- If the child has an effective cough, encourage coughing and continually reassess for clinical deterioration or relief of the obstruction.
- If the child has *no* effective cough, or severe respiratory distress, obstructed breathing, or central cyanosis, manage as for a choking child.
- Position the infant head down and give up to five sharp back blows between the shoulder blades using the heel of the hand as shown in Fig. 1.3.

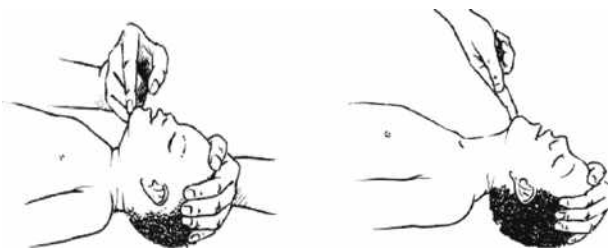


Fig. 1.2 (Left) Neutral position in infants. (Right) 'Sniffing' position in older child. Reproduced with permission from World Health Organization, *Pocket Book of Hospital Care for Children*, p. 9 © WHO, 2013. All rights reserved.

Fig. 1.3 (Left and middle) Back blows and chest thrusts to relieve airway obstruction in a choking infant. (Right) Heimlich manoeuvre in an older choking child. Reproduced with permission from World Health Organization, *Pocket Book of Hospital Care for Children*, pp. 7–8 © WHO, 2013. All rights reserved.

- If obstruction persists:
  - If <1yr, give five chest thrusts using two fingers (Fig. 1.3), similar to chest compressions, but sharper and at a slower rate.
  - If >1yr, if obstruction persists, perform the Heimlich manoeuvre (Fig. 1.3): stand behind the child and form a fist below the sternum with one hand. Place other hand over fist and pull both hands backwards and upwards. Repeat five times.
  - If obstruction persists, check infant's mouth for any obstruction that can be removed and repeat this sequence, starting with back blows.

Foreign body aspiration in an unconscious child

If an infant/child with a foreign body aspiration is unconscious, call for help, place them on a flat surface, and proceed with airway, breathing, circulation/coma/convulsions (ABC). Open the airway and remove any visible object and attempt five rescue breaths. If no response, proceed with chest compressions as detailed on ➲ Foreign body aspiration in a choking, conscious child, p. 8. When you reassess A, check for any removable foreign body. If obstruction has been relieved, continue giving rescue breaths until the child is breathing spontaneously.

Circulation and shock

The cause of shock needs to be considered before treatment commences. There are several broad causes that must be considered, namely, dehydration, anaemia (including haemorrhage), sepsis, the presence of underlying malnutrition and dengue. Dehydration needs treatment with Plan C (p. 235), anaemia requires blood (p. 11), sepsis must be managed with cautious aliquots of fluid, a child with malnutrition is treated according to WHO guidelines (p. 12) and dengue requires a separate protocol.

Shock has several definitions. Use 'severely impaired circulation' for those with the three signs of shock as defined by WHO, and impaired circulation for when there are less than three signs present.

- Remember ABC and give oxygen (O_2); *shock is an emergency* (Box 1.8).
- Assess for WHO-defined shock (cold hands *and* CRT >3s, *and* weak, fast pulse).
- Insert IV line (blood for haemoglobin (Hb)/haematocrit, glucose and cross-match).
- If unable to establish peripheral IV access quickly, insert external jugular or intraosseous line (Fig. 1.4), whichever is quicker.
- Fluid resuscitate for WHO-defined shock according to guidelines listed below, unless severely malnourished, which is managed differently (➲ Management of shock in children with severe malnutrition, p. 12).
- Stop bleeding; look for severe palmar pallor (severe anaemia, Box 1.9).
- Ensure child is warm.
- Monitor blood glucose levels while fluid resuscitating.

WHO recommendations for children who fulfil WHO definition of shock and are NOT severely malnourished

Give fluid resuscitate rapidly

- Give 20mL/kg bolus (normal saline or Ringer's lactate) as rapidly as possible, then reassess.
- If no improvement, give a second 20mL/kg fluid bolus (blood 20mL/kg over 30min if child is bleeding and it is available) then reassess.
- If still no improvement and signs of dehydration or shock, give a third 20mL/kg bolus as rapidly as possible. Otherwise, management is guided by the working diagnosis.

If improvement occurs at any stage (pulse slower, CRT faster)

- Assess need for rehydration.
- If no rehydration needed, give maintenance IV fluids.
- If dehydrated or history of profuse diarrhoea, give 70mL/kg Ringer's lactate or normal saline over 5h if <12mths and over 2.5h if 12mths–5yrs.
- Continue to assess the child every 1–2h. Some children may deteriorate after initial recovery.
- Give oral rehydration solution (ORS) (➲ ORS, p. 279) 5mL/kg/h as soon as child can drink.
- Follow appropriate treatment plan A, B, or C for dehydration (➲ Diarrhoeal diseases, p. 235) based on this assessment.

Box 1.8 Treatment of shock

A large randomized controlled trial (RCT) comparing fluid bolus resuscitation to IV maintenance fluid in children in Africa with clinical features of shock, showed ↑ mortality in those treated with fluid boluses. The study did not include children with hypotension, severe acute malnutrition (SAM), or gastroenteritis. The study also showed that WHO-defined shock was rare in the population studied.

Children with WHO-defined shock should be resuscitated according to WHO guidelines (➲ p. 10). For children with gastroenteritis, rehydrate according to WHO guidelines (➲ General management of dehydration, p. 272) and for children with SAM, treat shock as per WHO guideline (➲ Management of shock in children with severe malnutrition, p. 12). In children with some features of shock, but not fulfilling the WHO definition, treatment of their underlying condition is the priority. Maintenance fluids should be given, and any additional fluids given with great caution.

Data from Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; 364(26): 2483–95. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1101549

Box 1.9 Children with severe anaemia and shock

These children need red blood cells. Give maintenance fluids while waiting for blood. Resuscitate as required per guidelines on ➲ p. 10, while awaiting urgent blood for transfusion.

- Obtain blood for Hb/haematocrit, cross-match (and rapid malaria test in endemic areas) in all children with severe palmar pallor.
- If Hb <4g/dL, or haematocrit <12%, or Hb result not available quickly and there are clinical signs of severe anaemia, transfuse 20mL/kg whole blood. We now have the TRACT study results that confirmed 20mL/kg whole blood in febrile severe anaemia but 30mL/kg in afebrile children with severe anaemia. Also whole blood and packed cells gave similar 28 day outcomes. See https://www.nejm.org/doi/10.1056/NEJMoa1900100?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed
- *In the presence of very severe palmar pallor and shock*, consider urgent transfusion with O −ve blood.

Box 1.10 Cardiac arrest

Unlike in adults, most arrests in young children are 1° respiratory arrests +/– 2° cardiac arrest. As a result, adequate ventilation alone is sufficient to maintain cardiac output in most cases, while the cause of the arrest is identified and treated.

If there is also cardiac arrest requiring chest compressions:

- Give a ratio of 3:1 compressions to breaths in neonates.
- Give a ratio of 15:2 in infants and children.

Drugs

If no response after 2min, administer IV or intraosseous adrenaline 0.1mL/kg of 1:10,000 solution (10 micrograms/kg) and continue chest compressions and ventilation. This may be repeated after 3–5min if there is no response. In newborns, the preferred access is through an umbilical vein catheter (UVC).

Management of shock in children with severe malnutrition

WHO recommends treatment for children with severe malnutrition, signs of shock, and who are lethargic or have lost consciousness. See ➔ Nutrition, p. 642, for treatment of dehydration in SAM.

- Signs of shock and dehydration are less reliable in children with severe malnutrition.
- Types of fluid, volumes, and rates of administration are different to those used in well-nourished children.
- 💣 Giving too much IV fluid can → overload if ↓ cardiac output. They cannot excrete Na^+ load.
- Never use diuretics to treat the oedema of kwashiorkor as this will extract fluid from the intravascular space only.

At the start of treatment

- Weigh the child (or estimate weight) to calculate fluid requirements.
- Record pulse rate (PR) and respiratory rate (RR).
- Assess and treat hypoglycaemia (5mL/kg of 10% dextrose). If unable to measure glucose, assume there is hypoglycaemia.
- *For WHO-defined shock*: infuse 15mL/kg IV fluid over 1h. Use Ringer's lactate with 5% glucose, WHO also recommends half-normal saline with 5% glucose, or half-strength Darrow's solution with 5% glucose but these are hypotonic solutions. Use Ringer's lactate if these are not available.
- Monitor PR and RR every 5–10min.
- If child deteriorates during IV rehydration (RR ↑ by 5/min or PR ↑ by 15/min or ↑ oedema or facial puffiness), stop the infusion.

If there are signs of improvement (PR and RR ↓)

- Repeat 15mL/kg IV bolus over 1h.
- Then switch to oral or NG feeds if not comatose. Give hourly feeds, 10mL/kg/h alternating ReSoMal with F75.

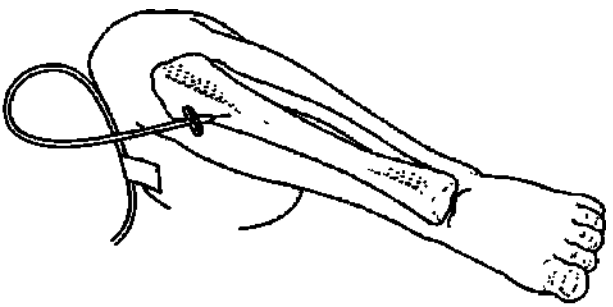


Fig. 1.4 Intraosseous needle insertion.

- Assess 2–3h hydration status and continue the hourly rehydration to a maximum of 10h (be careful not to overload).
- Continue feeding with F75.

Box 1.11 Intraosseous needle insertion

Intraosseous infusion is a quick, safe, and reliable method of giving fluid, blood, and drugs when it is not possible to establish peripheral venous access. The usual site of insertion is the proximal tibia (Fig. 1.4):

- Place padding under the child's knee so that it is flexed ~30° with the heel resting on the bed.
- Identify the insertion site 1–2cm below the tibial tuberosity, midway between the anterior ridge of the tibia and its medial edge.
- Use a dedicated intraosseous or bone marrow aspiration needle (15–18 gauge (G) or, if not available, 21G); if neither is available, a 21G or 18G hypodermic needle may be used in young children.
- Clean the skin with antiseptic solution; infiltrate local anaesthetic if the child is conscious.
- Stabilize the leg, grasping thigh and knee above and lateral to the cannulation site with non-dominant hand, taking care to keep hand away from cannulation site to avoid needlestick injury.
- Using aseptic technique, insert needle with point angled slightly away from the joint space and bevel pointing towards foot.
- Advance needle using a gentle, but firm twisting or drilling motion, until there is a sudden ↓ in resistance as it enters marrow cavity; needle should stand upright firmly in the bone.
- Remove the stylet, attach a syringe, aspirate marrow contents (looks like blood), and flush with normal saline to confirm needle is in marrow cavity. Blood from marrow aspirate may be sent for full blood count (FBC), biochemistry, malaria slide, and culture. If sent for cross-match, ensure the laboratory knows that it is a marrow aspirate.
- Apply dressing and secure needle in place. It is now ready to use.
- Stop the intraosseous infusion as soon as venous access is available.
- Do not leave needle in one site >6–8h.

Contraindications

Infection at the insertion site; fracture of the bone.

Alternative sites of insertion

Distal femur, 2cm above the lateral condyle (~1–2cm proximal to the superior border of the patella), slightly lateral to anterior ridge.

If there are still no signs of improvement

- Give maintenance IV fluids while waiting for blood.
- Transfuse 10mL/kg fresh whole blood slowly over 3h; give packed cells if fluid overload/heart failure; consider furosemide during transfusion.
- Start frequent small feeds with F75, or alternative low lactose and low osmolarity preparation (➲ Nutrition, p. 683).

In all cases, proceed to full assessment and management of severe malnutrition, incl. broad-spectrum antibiotics (➲ Diarrhoeal diseases, p. 233).

Coma and convulsions

The presence of coma or convulsions is an emergency.

Manage airway, breathing, and circulation

See ➲ Emergency management of the sick child—ABC, p. 8., assess and treat hypoglycaemia.

It is important to know what anticonvulsants are available locally and have a protocol for the timing and sequence of drugs to be given if seizures do not stop rapidly. The following sequence is commonly given.

If convulsing

- Give diazepam 0.5mg/kg rectally or midazolam (buccal) 0.3mg/kg (1–6mths), 2.5mg (6mths–1yrs), or 5mg (1–5yrs).
- If still convulsing after 10min, give second dose of diazepam or midazolam, or if IV access, diazepam 0.25mg/kg IV.
- If still convulsing after a further 10min, give paraldehyde 0.3–0.4mL/kg rectally, or phenobarbital 15–20mg/kg IV (as slow infusion over 20min) or intramuscularly (IM). (*Note*: peak concentration reached 1–4h after IM administration.) In infants <2wks old, give phenobarbital 20mg/kg as slow IV infusion.
- To prevent aspiration, avoid oral medications until the convulsions have terminated and the child is alert.

Note: seizures, especially in neonates and children with malaria, may be very subtle, comprising one or more of irregular respiration, nystagmus, or twitching of extremities or lips.

If unconscious

- Position in the left lateral 'recovery' position. If head or neck trauma is suspected, stabilize the neck first and keep the child lying on their back.
- Assess and treat the treatable: hypoglycaemia, poisoning, diabetes mellitus, septicaemia/meningitis, or herpes simplex encephalitis.

Hypoglycaemia

Assess and treat hypoglycaemia

- If lethargic or unconscious, measure blood glucose.
- If unable to measure glucose quickly, or if blood glucose <2.5mmol/L in a well-nourished child (<3mmol/L in severe malnutrition), give 5mL/kg 10% glucose rapidly IV; 2mL/kg for neonate.
- If alert, treat hypoglycaemia with 10mL/kg milk or 10% glucose by mouth or NG tube (NGT).
- Recheck blood glucose after 2h.

Nutritional status

Assess and treat severe malnutrition (➲ Nutrition, p. 683).

Further assessment and diagnosis

After triage, assess fully. Common acute problems in children are:

- Lethargy, ↓ level of consciousness, or convulsions.
- Cough, wheeze, or difficulty breathing.
- Diarrhoea.
- Fever.

Common problems that present less acutely include:
- Chronic cough ≥30d.
- Fever lasting >7d.

Major differential diagnoses for each clinical presentation

Causes of lethargy, impaired consciousness, or convulsions
- Meningitis (➔ Neurology, p. 429) or encephalitis.
- Cerebral malaria (➔ Malaria, p. 33).
- Febrile convulsions (Box 1.12).
- Hypoglycaemia (➔ Hypoglycaemia, p. 14).
- Head injury (➔ Neurology, p. 429).
- Poisoning/overdose (➔ Poisoning and envenoming, p. 871).
- Sepsis (unlikely to cause convulsions unless meningitis).
- Shock (unlikely to cause convulsions).
- Acute glomerulonephritis with encephalopathy (➔ Renal medicine, p. 403).
- Diabetic ketoacidosis (➔ Endocrinology and biochemistry, p. 537).

Causes of difficulty breathing +/– cough
- Pneumonia (➔ Chest medicine, p. 180).
- Severe anaemia.
- Malaria (➔ Malaria, p. 33).
- Cardiac failure (➔ Cardiovascular medicine, p. 365).
- Congenital heart disease.
- Inhaled foreign body (➔ Emergency management of the sick child—ABC, p. 8).
- Tuberculosis (TB) (➔ Tuberculosis, p. 151).
- Pertussis (➔ Chest medicine, p. 200).
- Prematurity (➔ Surfactant deficiency, p. 24).
- Be alert for acidosis and meningitis.

Causes of wheeze
- Asthma (➔ Chest medicine, p. 214).
- Bronchiolitis (➔ Chest medicine, p. 197).
- Viral upper respiratory tract infection (URTI).
- Pneumonia (➔ Chest medicine, p. 180).
- Inhaled foreign body.
- Lymph node (LN) compressing a bronchus (➔ Emergency management of the sick child—ABC, p. 8).

Causes of diarrhoea

See ➔ Diarrhoeal diseases, p. 233.
- *Infections*: viral, bacterial, and parasitic.
- Severe malnutrition.
- Malabsorption.
- Antibiotic related diarrhoea.
- Intussusception (Box 1.13).

Causes of fever without localizing signs

In most children with fever, cause is clinically apparent. Examine upper airways (URTI, otitis media, tonsillitis) and joints (septic arthritis), as well as the major systems (pneumonia, meningitis). Examine skin for infection or a rash (e.g. measles). In absence of localizing signs, consider:

- Malaria (➲ Malaria, p. 33).
- Bacteraemia/septicaemia incl. typhoid (Box 1.14).
- Urinary tract infection (UTI).

Causes of chronic cough

- TB (➲ Tuberculosis, p. 151).
- Asthma (➲ Chest medicine, p. 214).
- Persistent infection, e.g. following pertussis (➲ Chest medicine, p. 200).
- Inhaled foreign body (➲ Chest medicine, p. 175).
- Bronchiectasis (➲ Chest medicine, p. 222).
- Lung abscess (➲ Chest medicine, p. 204).
- Recurrent pneumonia or HIV-associated lung disease (➲ HIV/AIDS, p. 185).
- Recurrent aspiration.

Differential diagnosis of fever lasting >7d

Diagnosis is often difficult. Many children will have already been empirically treated and diagnostic facilities may be limited. A detailed clinical assessment is essential. Causes will vary in different regions. A carefully considered trial of treatment for the most likely cause may be necessary if a secure diagnosis cannot be made.

Consider

- Partly treated or (less likely unless in SE Asia), drug-resistant malaria.
- Occult abscess (e.g. liver, psoas, retroperitoneal, lung).
- Typhoid and non-typhi *Salmonella* infection (Box 1.14).
- Infective endocarditis (➲ Cardiovascular medicine, p. 394).
- Rheumatic fever (➲ Cardiovascular medicine, p. 392).
- TB (➲ Tuberculosis, p. 151).
- Brucellosis (in endemic areas) (➲ Multisystem diseases and infections, p. 768).

Box 1.12 Febrile convulsions

- Occur in children aged 6mths–6yrs.
- Generalized tonic or tonic–clonic seizure lasting up to 5min during a febrile illness.
- Full neurological recovery.
- Generally benign.
- May have a family history.
- In a minority of children may recur in the same or subsequent illness.

More serious cause (e.g. meningitis, cerebral malaria, encephalitis, brain abscess) suggested by:

- Prolonged seizures (>30min).
- Multiple or focal seizures.
- Persistent ↓ consciousness or neurological abnormalities.
- Age <6mths or >6yrs.

If in doubt, perform full septic screen including lumbar puncture (LP).

- Visceral leishmaniasis (in endemic areas) (➔ Multisystem diseases and infections, p. 794).
- Malignancy (esp. leukaemia or lymphoma).

Box 1.13 Intussusception

- Invagination of part of intestine into lumen of adjoining bowel.
- Important cause of intestinal obstruction in children aged 2mths–5yrs (peak incidence 4–10mths).
- Classically presents with recurrent, colicky, abdominal pain, vomiting, and bloody 'red currant jelly' stool; may palpate a sausage-shaped abdominal mass.
- Abdominal X-ray (AXR) may show soft tissue mass displacing loops of bowel; barium enema, a filling defect; and ultrasound scan (USS), a 'target lesion'.
- Urgent intervention can prevent bowel ischaemia and perforation: reduce with air/contrast enema; if this fails, operate.
- Treat shock, sepsis, or electrolyte derangement.

Box 1.14 Bacteraemia and septicaemia

- Common among children in the tropics.
- Underdiagnosed and overtreated where there are no facilities for blood culture.
- Often there is a focus of infection (e.g. pneumonia, meningitis, soft tissue infection), but sepsis may occur without a focus, or a focus may develop later.
- Typhoid and non-typhoid *Salmonella* infections are a cause of sepsis without localizing signs; a similar syndrome may occur with other organisms, esp. in children with severe malnutrition or HIV.
- All children with sepsis should be admitted and started on empiric parenteral antibiotics according to national guidelines, e.g. ampicillin (or benzylpenicillin) and gentamicin (ideally after blood cultures), during investigations.
- Malaria may be accompanied by bacterial sepsis.

Non-typhi Salmonella (NTS) infection

- NTS infections are a common cause of childhood bacteraemia.
- Risk factors incl. malnutrition, malaria, HIV, and sickle cell disease.
- Children may present with acute infection, or subacute or prolonged fever without localizing signs, but focal signs and/or diarrhoea occur; splenomegaly is common.
- First-line antibiotics (e.g. penicillin) do not cover NTS. Treat with ciprofloxacin or ceftriaxone. Multidrug resistance is increasing.

Typhoid (Salmonella typhi) in children

- Recent ↑ cases in Eastern and Southern Africa, often affecting 8–15yr-olds.
- Headache, fever, constipation, and abdominal pain. Untreated may → intestinal perforation. Complications: cachexia, collections of pus that need drainage, myocarditis, and encephalopathy.
- Treat is with ciprofloxacin or ceftriaxone; multidrug resistance is increasing.

The sick young infant

All young infants should be given priority, even in the absence of emergency signs. Infants <2mths are vulnerable, and their illnesses may rapidly → death.

Assessment of the sick young infant

Symptoms and signs are often subtle and non-specific and >1 illness may coexist.

Check for:

- *Danger signs* (Box 1.15): indicating possible septicaemia, pneumonia, or meningitis requiring immediate treatment.
- *Focal signs of infection*: incl. joint/limb swelling, ↓ limb movement, or tenderness (osteomyelitis or septic arthritis); periumbilical hyperaemia +/– purulent discharge; purulent ear discharge; skin infection. Suspect meningitis if child has convulsions or is irritable with high-pitched cry, ↓ feeding, lethargy/unconscious, or bulging/tense anterior fontanelle. *Note*: neck stiffness and a bulging fontanelle are late signs of meningitis in young infants.
- *Feeding problems and weight*: check if sucking well and weight is adequate for age. Refusal of feeds or inability to suck may be due to sepsis, cardiac or respiratory problems, or oral thrush. In an infant who feeds well, but has low weight for age, look for underlying problems, e.g. metabolic disorders or congenital heart disease.
- *Signs of dehydration* (p. 6): ↓ intake, ↑ fluid loss from diarrhoea, vomiting or tachypnoea may ↑ dehydration. Diarrhoea is less common in breastfed infants of this age.
- *Immunization status*: is the child up to date with the national immunization schedule?
- *Congenital malformations*.

Box 1.15 Danger signs in young infants

- ↓ activity or lethargy.
- Poor feeding.
- Vomiting.
- Convulsions, usually subtle or focal.
- Bloody diarrhoea.
- Fever (axillary temp >37.5°C, or rectal >38°C), less common in this age group, but may indicate serious bacterial infection.
- Hypothermia (axillary <35.5°C or rectal <36°C).
- Pallor, jaundice, or cyanosis.
- Tachypnoea (RR ≥60 breaths/min) or ↓ RR (<20/min) or apnoea (no breathing for >15s).
- Severe chest wall indrawing (minimal intercostal indrawing may be normal in young infants in absence of other respiratory signs).
- Nasal flaring, grunting, and head nodding.
- Irregular respiration.
- Bulging/tense fontanelle when not crying.

Emergency treatment of the sick young infant

Establish regular respiration and heart rate. Resuscitation is usually successful if promptly performed.

Airway

Ensure patent airway by careful suctioning and correct positioning of the neck: place a towel under the shoulders to allow the neck to drop to a neutral position or just minimal extension with chin lift; do not hyperextend the neck (Fig. 1.5).

Fig. 1.5 Correct position of the neck for ventilation. Reproduced with permission from World Health Organization, *Pocket Book of Hospital Care for Children*, p. 48 © WHO, 2013. All rights reserved.

Breathing

Look, listen, and feel for 10s. If breathing is irregular, shallow, or absent, commence BVM ventilation with O_2, ensuring mask covers nose and mouth. Check pulse every 2min. Use room air for newborn or if O_2 is not available. If the child is breathing, but cyanosed or RR >60/min, give O_2.

Circulation

Check for brachial pulse for up to 10s. If PR <60/min, absent, or not sure, commence chest compressions. After 2min give adrenaline if no cardiac output (Box 1.10). Combine chest compressions with ventilation in cycles of 15 compressions to 2 breaths (30:2 if there is no assistance). Use two finger tips over lower third of sternum or both thumbs with hand encircling chest and compress 1/3 of anteroposterior diameter. Aim for 90 compressions and 10 breaths/min. *For neonates*, give 3 compressions for 1 breath every 2s (90 compressions and 30 breaths/min); see algorithm for newborns (➲ Fig. 1.7, p. 23).

General measures in the management of sick young infants

Young infants with signs of serious illness (➲ p. 18) require admission to prevent complications and rapid deterioration. Direct treatment, incl. antibiotics (Box 1.16), at the specific clinical syndrome. In addition, all young infants require ongoing supportive care, which is crucial to survival even after recovery from the acute illness.

Feeding

Ensure continued regular feeding. Express breast milk and give by NGT if infant is unable to suck, or by cup and spoon as soon as infant is able to take oral feeds. Stop oral intake if abdominal distention, severe vomiting, frequent convulsions, or respiratory distress. Treat hypoglycaemia with IV 10% glucose 5mL/kg or 10mL/kg (2mL/kg for a neonate) via NGT and continue regular feeds or IV fluids.

Fluid requirements

Total amount, given as oral or IV in neonates with feeding difficulties: day 1 (60mL/kg/d), day 2 (90mL/kg/d), day 3 (120mL/kg/d), thereafter (150mL/kg/d). May ↑ to 180mL/kg/d. If on phototherapy, increase ×1.2–1.5.

Fluid therapy

Assess hydration status and give ORS or IV fluids according to WHO guidelines (➲ Diarrhoeal diseases, p. 233).

Temperature control

Keep infant dry and well wrapped, incl. bonnet and booties. Maintain environmental temperature of at least 25°C. Avoid excessive exposure during examination and procedures as this may → chilling. Use incubators when available to allow easy observation with minimal handling of baby in addition to thermal control. Use skin-to-skin care (kangaroo mother care (KMC), see ➲ Box 1.17, p. 22) when the infant is stable. If there is fever, remove clothes and expose.

Oxygen therapy

Indications for O_2 therapy incl. central cyanosis, grunting, severe lower chest wall indrawing, difficulty in feeding due to respiratory distress, and head nodding. Stop O_2 if saturations >90% in room air.

Treatment of convulsions

Neonates (<2wks old)

IM phenobarbital 20mg/kg IM or very slow IV stat; if maintenance is required, give 5mg/kg/d oral/IM

Infants 2wks–2mths old

Rectal diazepam 0.5mg/kg, repeat at 10min if convulsions persist (or give IV diazepam 0.25mg/kg). If still convulsing after another 10min give third dose of diazepam or rectal paraldehyde 0.3–0.4mL/kg. Monitor closely, as diazepam has ↑ half-life in infants.

Monitoring

Observe all infants at least every 6h for improvement or deterioration. Severely ill infants require frequent monitoring. Review infants 15–30min after any intervention.

Outpatient treatment

Infants with non-bloody diarrhoea, and some or no signs of dehydration (➲ Assessment of dehydration in children with diarrhoea, p. 277), or poor weight gain due to feeding mismanagement, may be treated as outpatients. The mother should be informed of danger signs that require urgent review. Local bacterial infections without constitutional symptoms are common and may be treated as an outpatient, with follow-up at short intervals because of the risk of rapid progression to septicaemia. These include omphalitis (*without* hyperaemia of surrounding skin), skin sepsis (if only a few skin pustules), paronychia, and mild conjunctivitis.

Box 1.16 Antibiotic therapy of infections in young infants

When choosing antibiotics, be aware of local data about prevailing organisms and antibiotic sensitivities.

- *Sepsis or pneumonia*: give ampicillin 50mg/kg IV/IM qds* (or benzylpenicillin 50,000U/kg qds*) plus gentamicin 7.5mg/kg* IV/IM od. Cefotaxime 50mg/kg IV/IM qds* or ceftriaxone 80mg/kg IV/IM od*† are alternatives. If *Staphylococcus aureus* infection suspected (e.g. nosocomial sepsis, soft tissue infection), give cloxacillin 50mg/kg IV qds* or cefuroxime 25mg/kg tds, plus gentamicin. Treat until child has remained well for 4d.
- *Meningitis*: give cefotaxime 50mg/kg IV/IM qds* or ceftriaxone 100mg/kg IV/IM od. Treat for a minimum of 14d, or 21d if Gram –ve bacterial meningitis proven or suspected.
- *Focal bacterial infections*: amoxicillin, or a cephalosporin.
- *Conjunctivitis*: teach mother to clean child's eyes with saline or clean water +/– apply topical antibiotic. Review child after 2d.
  - *Ophthalmia neonatorum* (➲ Conjunctivitis, p. 578; ➲ Gonorrhoea, p. 670)— a severe, suppurative conjunctivitis, often with associated blepharitis, that occurs in neonates, particularly in the 1st week of life, and may → permanent blindness if not treated. Caused by *Neisseria gonorrhoea* or *Chlamydia trachomatis* perinatally; other organisms incl. *S. aureus*. Gram stain of the discharge may demonstrate Gram −ve diplococci (*N. gonorrhoea*). If so, give ceftriaxone 50mg/kg IM as a single dose, treat the parents presumptively for *N. gonorrhoea* (➲ Gonorrhoea, p. 670).

* Doses in 1st week of life: ampicillin 50mg/kg bd; benzylpenicillin 50,000U/kg bd; gentamicin 5mg/kg od if normal birth weight, 3mg/kg od if low birth weight; cefotaxime 50mg/kg tds in term neonates, bd in premature neonates; cloxacillin 25–50mg/kg bd.

† Ceftriaxone may cause jaundice by displacing bilirubin from albumin: in practice, this is seldom a problem.

Neonatal notes

Newborns and neonates (<28d) have special considerations beyond those of the sick young infant, and are the subject of specific WHO recommendations (https://apps.who.int/iris/handle/10665/259269).

Resuscitation at birth differs from young infants, in particular with the need for inflation breaths (can be undertaken with air) after delivery. See summary diagram for special features (Fig. 1.7, p. 23).

Care after delivery is also important and KMC (Box 1.17) can help with this. Most at risk are those with low birth weight (LBW) or preterm delivery. Common problems are respiratory distress syndrome, apnoeas, sepsis (see Box 1.16, p. 21, for antibiotic therapy), jaundice, hypothermia, and hypoglycaemia. A common complication is neonatal encephalopathy (NE) (Box 1.19, p. 28), with ↑ perinatal asphyxia where access to emergency obstetric care is limited.

Box 1.17 Kangaroo mother care

KMC is recommended routinely for stable newborns ≤2000g and involves direct skin-to-skin care of the infant. The baby is placed naked (except for nappy, hat, and booties) directly on the mother's bare chest (Fig. 1.6), and strapped in place to get warmth, while the mother goes about her regular activity. KMC is preferred to an incubator; it ↑ weight gain and ↓ infections, apnoeas, and length of hospital stay. KMC helps establish breastfeeding, and → mother/child bonding. Close family members, incl. the father, can also provide KMC.

Fig. 1.6 Position for kangaroo mother care of young infant. Reproduced with permission from World Health Organization, Pocket Book of Hospital Care for Children 2005: 59, with permission of WHO.

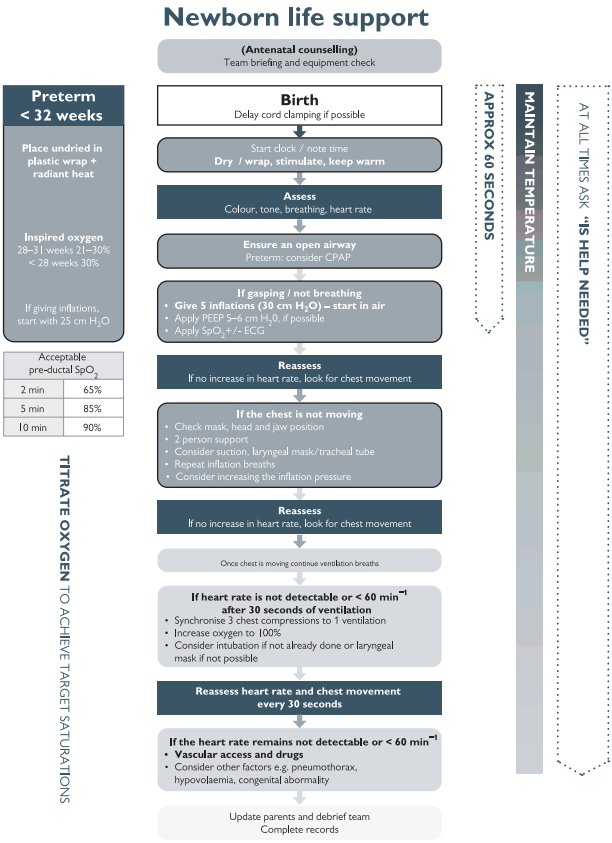


Fig. 1.7 Newborn life support. Note that there are special situations (e.g. meconium at delivery, preterm delivery). See the most uptodate guidance and algorithm at https://www.resus.org.uk/sites/default/files/2021-05/Newborn%20Life%20Support%20Algorithm%202021.pdf

*Dawson JA, Kamlin CO, Vento M, et al. Defining the reference range for oxygen saturation for infants after birth. *Pediatrics 2010* 125:e1340–7.

Reproduced with permission from the Resuscitation Council Guidelines (2010), with permission from the Resuscitation Council UK.

Low birth weight and prematurity

LBW infants may result from prematurity (most common) or intrauterine growth retardation (IUGR).

- LBW <2500g.
- Very low birth weight (VLBW) <1500g
- Extremely low birth weight (ELBW) <1000g.

Infants <1800g, born before 34wks' gestation or who are sick need admission. Stable babies should be in KMC with mother. Infants who are gaining weight on 3 successive days and are able to cup or breast feed and have no danger signs may be sent home.

Essential aspects of LBW care

- *Prevention of infection*: wash hands with soap and water each time infant is to be handled.
- *Temperature control* (➲ Hypothermia, p. 24): maintain the infant's axillary temperature >36.5°C.
- *Treatment of infection*: in many cases, premature labour is precipitated by an infection, hence preterm newborns should be empirically treated with ampicillin and gentamicin.
- *Feeding*: LBW babies are prone to hypoglycaemia and may not suck adequately. All babies should be put to the breast as soon after birth as possible and should be breastfed within 1h of birth; they may require additional expressed breast milk by cup and spoon or via NGT. Mothers should be shown proper latching-on techniques. Monitor weight gain. If necrotizing enterocolitis is suspected, stop all oral intake and give baby parenteral nutrition and broad-spectrum antibiotics, including anaerobic cover (metronidazole).
- *Vitamin K*: give 1mg IM if >2kg: 0.5mg if <2kg body weight.
- Be alert for danger signs: refer promptly to neonatal unit if present.

Problems associated with LBW

- Poor thermal regulation.
- Respiratory distress syndrome (surfactant is seldom available, often benefit from early continuous positive airway pressure (CPAP) or O_2).
- Feeding problems (inadequate intake, gastro-oesophageal reflux).
- Necrotizing enterocolitis.
- Neonatal jaundice.
- Metabolic problems (hypoglycaemia, acidosis, hypocalcaemia, fluid, and electrolyte imbalance).
- Apnoea.
- Patent ductus arteriosus.
- Vulnerable to infections and intraventricular bleeds.

Hypothermia

Hypothermia (body temperature <36.5°C) is a common problem of LBW infants, resulting from low environmental temperature or sepsis. It causes ↑ O_2 consumption, ↑ energy expenditure, and ↓ O_2 delivery to tissues.

- *Complications*: incl. hypoxia, acidosis, and hypoglycaemia; poor weight gain; ↑ capillary permeability; and respiratory distress due to ↓ surfactant production.

- *Treatment*: rewarm infant using warm clothing, incubator preheated to 35–36°C, heated mattress, or skin-to-skin care. Exclude sepsis.
- *Prevention*: nurse infants in warm environments. Avoid wet clothes and do not place infant on cold surfaces, e.g. X-ray plates and weighing scales.

Apnoea

Apnoeic episodes are common in LBW infants. May be accompanied by bradycardia if prolonged. Gentle physical stimulation often stimulates breathing, but respiratory stimulants are routinely given (caffeine or aminophylline) and occasionally ventilatory support may be required (Table 1.1). Seek underlying causes: infection, hypoxia, metabolic derangement, anaemia, or subtle seizures.

Table 1.1 Aminophylline for prevention of apnoeas of prematurity

Weight (kg)	Stat dose to load	Aminophylline solution	BD dose	Aminophylline solution
0.75–0.99	5mg	1mL	2mg	0.4mL
1.0–1.49	7.5mg	1.5mL	3mg	0.6mL
1.5–1.99	10mg	2mL	4mg	0.8mL

Dissolve 100mg tablets in 20mL of water, each mL contains 5mg of aminophylline.

Reproduced from Kawaza, Kondwani; Mzikamanda, Rizine; and Molyneux, E; Liz; *Care of the infant and newborn in Malawi (2017): The COIN Course - Participants Manual*, p. 98 © The Authors, 2017.

Neonatal jaundice

Jaundice occurs in >50% of neonates and is more common in LBW infants. Jaundice may be a sign of serious disease (e.g. infection; see Box 1.18), esp. if it occurs on day 1, is associated with fever, is deep (involves palms and soles), or lasts >14d (>21d if premature). Jaundice is also commonly physiological, but other causes should be first considered.

Severe jaundice may → *kernicterus* (neurotoxicity). In its mild form, there is lethargy and reduced feeding. Severe kernicterus → irritability, hypertonia +/– opisthotonos, and long-term neurological sequelae.

Assessment of jaundice

Serum bilirubin levels, depending on the maturity of the infant and the postgestational age, will direct management (Box 1.18).

If serum bilirubin cannot be measured, the Kramer chart can be used. However, the chart is less accurate.

Investigations for abnormal jaundice

Consider (if available) total serum bilirubin and conjugated/unconjugated bilirubin, FBC, maternal and infant blood group, Coombs test, glucose 6-phosphate dehydrogenase (G6PD) screen, thyroid function, syphilis serology, and abdominal USS.

	All babies who are jaundiced in the first 24 hours of life
Area 1 + 2	If preterm, low birth weight, or sick
Area 1 – 5	All babies including healthy term babies

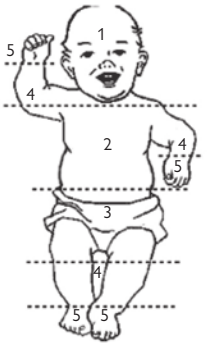


Fig. 1.8 The Kramer chart. Reproduced with permission from Kawaza, Kondwani, Mzikamanda, Rizine, and Molyneux, *Care of the infant and newborn in Malawi (2017): The COIN Course - Participants Manual*, p. 95, COIN Chart I Jaundice © The Authors, 2017.

Management of jaundice

Ensure adequate hydration and exclude serious causes (Box 1.18).

- Treat severe jaundice to prevent kernicterus (Table 1.2).
- *Phototherapy*: reduces jaundice by using ultraviolet light → photodegradation of bilirubin in the skin. Protect infant's eyes. Beware of dehydration, hypothermia, or hyperthermia. Other complications incl. diarrhoea and rash.
- *Exchange blood transfusion*: may be required for severe jaundice. Twice the infant's blood volume (i.e. 2 × 80mL/kg) is exchanged for fresh donor blood in 10–20mL aliquots via UVC. Low but definite risk attached to procedure.

Box 1.18 Common causes of neonatal jaundice

Jaundice starting <24h after birth

- Haemolysis (e.g. rhesus or ABO incompatibility; G6PD or pyruvate kinase deficiency; congenital spherocytosis).
- Infection (TORCH* organisms).

Jaundice starting from day 2 to week 2 after birth

- Physiological jaundice.
- Infection.
- Breast milk jaundice.
- Haemolysis.
- Severe bruising.

Jaundice persisting for >2wks after birth

- Biliary atresia.
- Infection.
- Neonatal hepatitis.
- May also be persistence of breast milk or physiological jaundice.
- Haemolysis.
- Congenital hypothyroidism.

*Toxoplasma; syphilis, varicella zoster virus (VZV), measles; rubella; CMV; herpes simplex.

Table 1.2 Indications for treatment of neonatal jaundice according to serum bilirubin concentration

	Phototherapy				Exchange transfusion			
	Healthy term baby		Preterm or risk factors		Healthy term baby		Preterm or risk factors	
	mg/day	µmol/L	mg/dL	µmol/L	mg/dL	µmol/L	mg/dL	µmol/L
Day 1	Any visible jaundice				15	260	13	220
Day 2	15	260	13	220	25	425	15	260
Day 3	18	310	16	270	30	510	20	340
Day >4	20	340	17	290	30	510	20	340

Neonatal encephalopathy

NE is a heterogeneous syndrome of neurological dysfunction in infants >35wks' gestation, in the first few days of life. The causes may be acute insults in the perinatal period or repeated injuries throughout pregnancy. One cause of NE is hypoxic-ischaemic encephalopathy (HIE) due to perinatal asphyxia → hypoxia, acidosis, and carbon dioxide (CO_2) accumulation around time of delivery. HIE accounts for much neonatal mortality and long-term morbidity, esp. in low-resource settings. HIE is largely preventable with improved obstetric care, prompt resuscitation, and supportive care of the neonate.

Assessment

Risk factors for NE are

- *Antepartum*: e.g. maternal—hypothyroidism, neurological disorders. Placental—haemorrhage, infection, infarction, pre-eclampsia. Fetal—IUGR.
- *Intrapartum*: e.g. prolonged second stage, abnormal lie, cord prolapse, failed vacuum extraction, infection, placental abruption.

Cause of NE is often unknown. See risk factors in Box 1.19. Indications of likely NE at birth include:

- Apgar scores ≤5 at 10min (Table 1.3).
- Resuscitation >10min before spontaneous respiration.
- Cord blood pH <7 or base excess >12mmol/L.

Prevention

Monitoring the mother in pregnancy and labour helps to predict infants at risk of NE. However, some babies who present with NE have not been exposed to known risk factors. Everyone involved in the delivery of babies should be skilled in newborn resuscitation, to ↓ morbidity and mortality from NE.

Box 1.19 Risk factors for neonatal encephalopathy

- *Maternal medical or obstetric factors*: hyper- or hypotension, heart failure, diabetes, severe anaemia, haemoglobinopathies, infections, respiratory illness (e.g. pneumonia, asthma), smoking, alcoholism, pre-eclampsia/eclampsia, primigravidity or grandmultiparity, induction of labour, sedation, analgesia, prolonged rupture of membranes, prolonged labour.
- *Fetal factors*: multiple gestation, prematurity or post-term, IUGR or large for gestational age, intrauterine infections, abnormal presentation, congenital abnormalities.
- *Placental factors*: abruptio placentae, placenta praevia, placental insufficiency, cord compression.

Complications of asphyxia and their management

Asphyxia may → multiorgan dysfunction.

- *Respiratory system*: persistent pulmonary hypertension and respiratory distress syndrome. Ensure good oxygenation.
- *Cardiovascular system*: myocardial damage → poor cardiac output. Monitor capillary refill and BP. Avoid fluid overload and give inotropes if necessary.

- *Gastrointestinal system*: risk of necrotizing enterocolitis. Avoid enteral feeding in first 24–48h (beware of hypoglycaemia!). With introduction of feeds, avoid hyperosmolar feeds and stasis.
- *Metabolic*: hypoglycaemia or hyperglycaemia may worsen hypoxic damage to the brain. Hyponatraemia, hyperkalaemia, hypocalcaemia, or acidosis may result; monitor blood glucose and electrolytes.
- *Renal function*: ↑ risk of urinary retention and renal failure. Monitor fluid intake, urine output, and urine specific gravity. Catheterize to differentiate between failure to produce or void urine.
- *Haematologic*: bone marrow suppression, neutrophil dysfunction, and coagulopathies. Monitor FBC for evidence of bleeding.
- *Brain*: encephalopathy results from hypoxia, cerebral oedema, ↑ intracranial pressure (ICP). Look for ↓ reflexes, abnormal muscle tone, seizures, varying degrees of altered consciousness. Treat seizures and irritability with phenobarbital.
- *Body temperature*: centrally driven hyperthermia is common and difficult to differentiate from sepsis.

General measures: ensure thermoneutral environment, adequate calories, and hydration, and treat neonatal jaundice.

Classification of NE

HIE is one cause of NE. It can be graded into:

- *Mild*: baby is irritable and responds excessively to stimulation, may have feeding difficulties, hyperventilation, or staring eyes.
- *Moderate*: baby shows abnormal tone and movements, cannot feed, and may have convulsions.
- *Severe*: baby has no spontaneous movements or response to pain; tone in limbs may fluctuate between hypotonia and hypertonia. Convulsions may be prolonged and often not respond to treatment. Multiorgan failure is present.

Prognosis of NE/HIE

- *Mild*: complete recovery can be expected.
- *Moderate*: if fully recovered by day 7, excellent long-term prognosis. If abnormalities persist >day 10, full recovery becomes unlikely.
- *Severe*: has a mortality of 30–40%; 80% of survivors have neurodevelopmental disabilities, esp. cerebral palsy.

Treatment

- Care is primarily symptomatic and supportive.
- Therapeutic cooling of term babies in intensive care settings with rigorous protocols has proven to ↓ morbidity from moderately severe perinatal asphyxia. Safety and applicability of this has not been fully established in resource-poor settings.

Table 1.3 APGAR score

	Score=0	Score=1	Score=2
Appearance (colour)	Pale/blue	Blue extremities	Completely pink
Pulse rate	Absent	<100/min	>100/min
Respiration	Absent	Slow, irregular	Regular, crying
Reflexes (grimace)	No response to stimulation	Grimace/feeble cry on stimulation	Cry/pull away when stimulated
Activity (muscle tone)	None/flaccid	Some flexion	Well-flexed legs resist extension

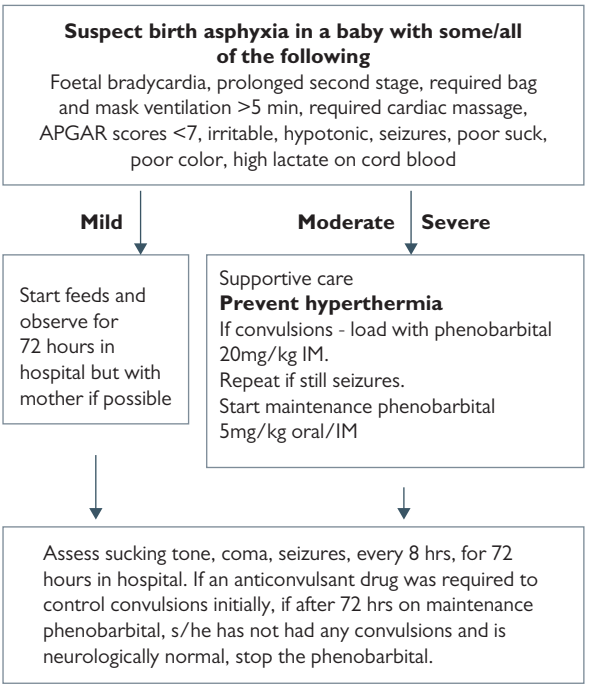


Fig. 1.9 Management of neonatal encephalopathy. Reproduced with permission from Kawaza, Kondwani, Mzikamanda, Rizine, and Molyneux, Liz, *Care of the infant and newborn in Malawi (2017): The COIN Course - Participants Manual*, p. 43 © The Authors, 2017.

Neonatal infection

Neonatal infection → directly to a quarter of all neonatal deaths in resource-poor settings, and high morbidity. Clinically diagnosed 'possible serious bacterial infection' (pSBI) was est. in ~6.9 million neonates in Africa, South Asia, and Latin America in 2012 and incl. meningitis, septicaemia, and lung infections. Rapid treatment is needed. The causative agents of neonatal serious bacterial infection differ depending on time of acquisition. Infections presenting early (days 0–6), or as a stillbirth, can be through transplacental transfer, e.g. syphilis, or from the mother's genital tract, e.g. *Strep. agalactiae* (GBS) or *Escherichia coli*. Other infections (usually horizontally acquired) typically present later (days 6–27), e.g. *Strep. pneumoniae*, *Strep. pyogenes*, *Staph. aureus*, and *Salmonella* spp. Hospital-acquired infections (HAIs) are ↑ caused by multidrug-resistant Gram −ve bacteria, e.g. *Klebsiella pneumoniae*, *Acinetobacter*, as well as *Staphylococcus* spp.

Diagnosis

In resource-poor settings, initial treatment and referral to hospital is guided by simple algorithms to diagnose pSBI, based on the presence of at least one clinical sign, which include: severe chest in-drawing, fever (>37.5°C), hypothermia (<35.5°C), no movement at all or only on stimulation, feeding poorly or not feeding at all, convulsions, and fast breathing (RR >60/min). Danger signs for young infants are also listed in ➔ Box 1.15, p. 18. Where available, pSBI should be investigated with microbiological cultures (blood, cerebrospinal fluid (CSF)) to confirm diagnosis and determine susceptibilities.

Treatment

Early treatment is critical. Use the ABC approach (➔ Treatment of sick child, p. 19): O_2 for respiratory support, KMC or an incubator for warmth, nutrition, and fluids by IV or NGT. Antimicrobial therapy: check local/national guidelines; WHO recommends first-line IV ampicillin (or penicillin) and gentamicin. Use cloxacillin instead of penicillin if staphylococcal infection is suspected. Third-generation cephalosporins are commonly used as alternatives. HAIs may require treatment with amikacin or meropenem.

Where treatment in hospital is not possible, WHO provides guidance, see https://apps.who.int/iris/bitstream/handle/10665/254502/WHO-MCA-17.01-eng.pdf?sequence=1

Prevention

Antenatal: maternal immunization (e.g. tetanus), treatment of syphilis if Venereal Disease Research Laboratory (VDRL) or rapid plasma regain (RPR) +ve, ART for HIV +ve mothers and intermittent preventive treatment in pregnancy (iPTP) and a bed net, in malarial areas.

Delivery: skilled HCW in attendance, clean and safe environment.

Postpartum: chlorhexidine gel applied to cord shortly after delivery; continued once daily for a week in the community. Hospital staff must have meticulous hand washing and hygiene. Mothers should receive hygiene education.

Congenital syphilis

All infants of seropositive (e.g. VDRL/RPR +ve) mothers should receive a 14d course of penicillin unless mother's treatment was documented complete and finished >4wks before delivery.

Signs and symptoms suggestive of syphilis

- Previous macerated stillbirth or hydrops fetalis, small-for-dates infant, jaundice, hepatosplenomegaly, nasal discharge, petechiae, desquamating rash on hands and feet, condyloma lata.
- In neurosyphilis, a LP may show ↑ protein, lymphocytes, and a +ve VDRL.
- Syphilis may be asymptomatic in neonates.
- In all cases, both parents should also be treated.

Congenital tuberculosis

A mother with TB diagnosed in the third trimester or shortly after delivery should receive TB treatment according to national guidelines. Her infant should be carefully examined for signs and symptoms of TB and treated accordingly. *Well children* should receive preventive treatment with isoniazid 10mg/kg daily for 6mths. BCG is deferred until completion of preventive treatment. Breastfeeding can continue as normal. A chest X-ray (CXR) is done at 6wks to confirm absence of infection. An infant with TB will need to receive full TB therapy.

Neonatal tetanus

This frequently fatal, preventable condition remains common in some resource-poor countries. *Clostridium tetani* usually infects the infant through the umbilical stump (due to poor hygiene or a tradition of applying various substances to the stump) or unsterile circumcision. The pathogenesis of tetanus is described on ➲ Neurology, p. 454.

Clinical features

Usually presents at 2–14d, but may occur later.

- Inability to open mouth (risus sardonicus).
- Refusal of feeds.
- Excessive crying.
- *Muscle rigidity and spasms*: provoked and spontaneous.
- Intact consciousness.

Diagnosis

This is a clinical diagnosis.

Treatment

- *Muscle relaxants*: oral diazepam 5mg/kg/d in divided doses via NGT.
- *For difficult-to-control spasms*:
  - IV diazepam 0.1–0.3mg/kg every 1–4h titrated to spasm frequency.
  - IV midazolam 0.06mg/kg/h is a suitable, but expensive alternative.
  - Rectal paraldehyde 0.3mL/kg titrated to spasms.
  - IV magnesium sulphate may also be useful.
- IM tetanus immune globulin 500U or equine anti-tetanus serum 10,000U single dose.
- Tetanus toxoid (in a different site) if >6wks old.

- *Antibiotics*:
  - Metronidazole (drug of choice) or penicillin or erythromycin.
  - Add broad-spectrum antibiotics (e.g. ceftriaxone) only if sepsis suspected.
- *Supportive care*:
  - Nutritional support.
  - Nurse in quiet, dark environment to prevent provoked spasms (but ensure adequate clinical supervision).
  - Ensure clear airway and give ventilatory support if needed.

Poor prognostic factors

- Incubation period <7d.
- Period of onset <24h.
- Associated pneumonia.

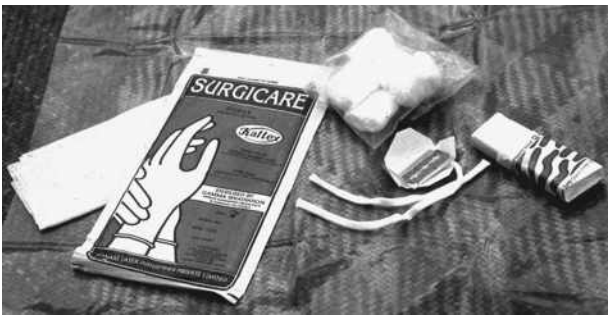


Fig. 1.10 Traditional birth attendant kit for home deliveries. As well as illustrated instructions, the kit contains (all sterile) plastic sheet for delivery, soap, towels, gloves, cotton wool, umbilical cord ties, and razor blade. Reproduced with permission from the Kenya Ministry of Health, with permission.

Public health note: prevention of neonatal tetanus

- Maternal education about cord care and hygiene.
- Immunization of all women in childbearing age with tetanus toxoid (➲ Tetanus immunization schedules, p. 909).
- Hygienic delivery and cord care practices.

Chapter 2

Malaria

Kevin Marsh

Introduction

Malaria, a protozoan infection transmitted by anopheline mosquitoes, is the most important parasitic disease of humans. ~3.3 billion people in endemic areas are at risk of malaria and ~250 million clinical cases occur annually. Around half a million die annually, largely African infants and young children. There are five human malaria parasite species (*Plasmodium falciparum*, *P. vivax*, *P. ovale*—of which there are two subspecies—and *P. malariae*). Human infection with the macaque malaria species *P. knowlesi* is increasingly recognized in Southeast Asia. The clinical manifestations of malaria vary greatly, depending on a number of factors including the infecting malaria species (*P. falciparum* causes the vast majority of severe disease), transmission intensity, and the degree of resistance (acquired and genetic) of the host. Recently several countries have become free of malaria [e.g. 2014 Algeria 2019 Kyrgzstan 2016 Uzbekistan 2018 Argentina 2019 Paraguay 2018 Maldives 2015 Sri Lanka 2016 El Salvador 2021]. In addition, transmission has decreased in large areas of Africa, Asia and South America. Artemisinin resistance is a growing threat.

Life cycle and transmission

The life cycle of the malarial parasite alternates between the sexual cycle in the invertebrate host (the female *Anopheles* mosquito) and the asexual cycle in the human host.

- Transmission occurs when the mosquito, requiring blood for the development of her eggs, bites the human host and injects motile sporozoites (Fig. 2.1) which enter the bloodstream and then home to and invade hepatocytes, where they develop into liver schizonts.
- When each schizont ruptures, thousands of merozoites are released that invade RBCs and initiate the part of the cycle responsible for all the clinical manifestations of the disease.
- Either immediately after release from the liver or (in the case of *P. falciparum*) after several asexual cycles, some parasites develop into longer-lived, morphologically distinct sexual forms, gametocytes.
- Male and female gametocytes ingested by mosquitoes taking a blood meal combine to form a zygote, which matures into an ookinete that encysts in the gut wall.
- There an oocyst develops, expanding by asexual division until it bursts, releasing numerous sporozoites that migrate to the salivary glands. These await inoculation into a human host when the mosquito next feeds.

Incubation periods

- *P. falciparum* 7–14d usually, but may be longer in those with partial immunity or those on inadequate prophylaxis (typically up to 6wks; very exceptionally >1yr).
- *P. vivax* 12–17d, but may relapse months or years later as a result of the reactivation of a dormant form in the liver called the hypnozoite.
- *P. ovale* 15–18d but may relapse months or years later as a result of the hypnozoite.
- *P. malariae* 18–40d and has no hypnozoite form. *P. malariae* may persist asymptomatically in blood at very low levels for years.

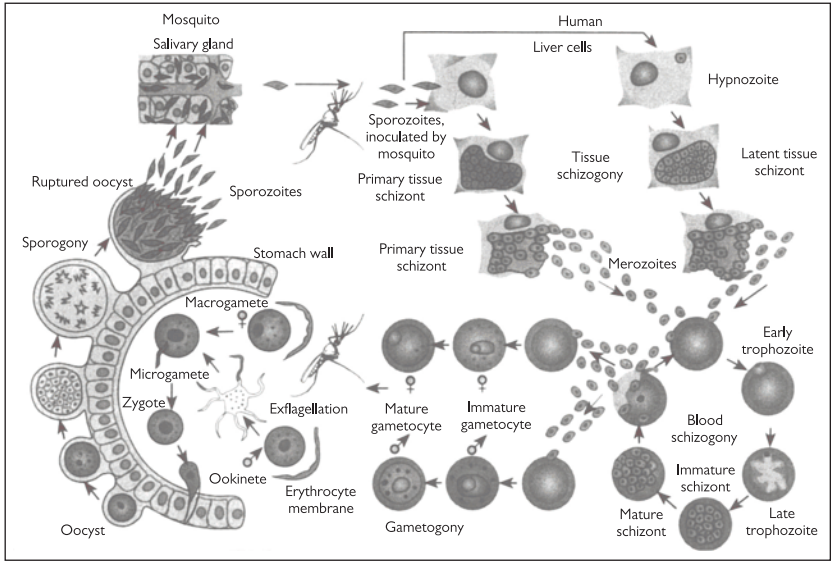


Fig. 2.1 The malaria life cycle (hypnozoite stage is limited to *P. vivax* and *P. ovale*). Reproduced with permission from David A. Warrell, Timothy M. Cox, and John D. Firth, *Oxford Textbook of Medicine* 5e, 2010, Oxford University Press, Redrawn by permission of F. Hoffman-la- Roche Ltd, Basel, Switzerland.

Epidemiology

Malarial transmission depends upon a number of factors including:

- Mosquito longevity (lifespan).
- Ambient temperature (shortens the cycle in the mosquito).
- Population density of both mosquitoes and humans.
- Mosquitoes' human-biting habit.
- Host immune response.
- Whether the drugs used in treatment have any activity against gametocytes.

In endemic areas (Fig. 2.2), the entomological inoculation rate is used as an indicator of transmission intensity. Because transmission is hard to measure, it is often estimated using the parasite rate (% of the population who are +ve for malarial parasites on blood film).

Two distinct patterns of malarial transmission emerge, which represent extremes:

- Stable malaria, where there is intense all-year round transmission. The disease predominantly affects young children and pregnant women. Adults might be +ve on blood film, but are rarely ill with malaria.
- Unstable malaria, in which the disease affects all ages and occurs in areas of seasonal or low transmission.

There is a concern that malaria control interventions in stable areas that ↓ transmission, but do not eliminate the disease, may ↓ the development of naturally acquired immunity in the population, → a pattern of unstable disease.

Protection against malaria

Many innate factors confer resistance against infection. Acquired resistance to malaria is slow to develop and the immune mechanisms involved are still unclear.

Innate immunity

Falciparum malaria remains the best example of an agent that selects for genetic polymorphisms that provide partial protection against severe disease. Certain genetic variants of the red blood cell (RBC), notably sickle cell trait, G6PD deficiency, thalassaemia trait, and ovalocytosis, may partially protect against severe disease. The lack of Duffy antigen (the receptor for merozoites of *P. vivax*) on RBCs in many African populations accounts for the rarity of this parasite in Africa (except areas such as Mauritania and Ethiopia).

Acquired immunity

Requires repeated exposure to malarial infection, possibly with differing genetic variants of parasite. In areas of intense, stable transmission, neonates are usually protected by maternal antibodies for first ~6mths of life, followed by a period of ↑ susceptibility, during which immunity to severe disease is slowly acquired. In such areas, most deaths occur by 5yrs. Individuals remain susceptible to non-life-threatening febrile episodes, which by adulthood are uncommon. Adults remain susceptible to asymptomatic infection for life. Without reinfection, immunity eventually ↓ over a period of years. Pregnancy, severe illness, and surgery may also lead to ↓ immunity.

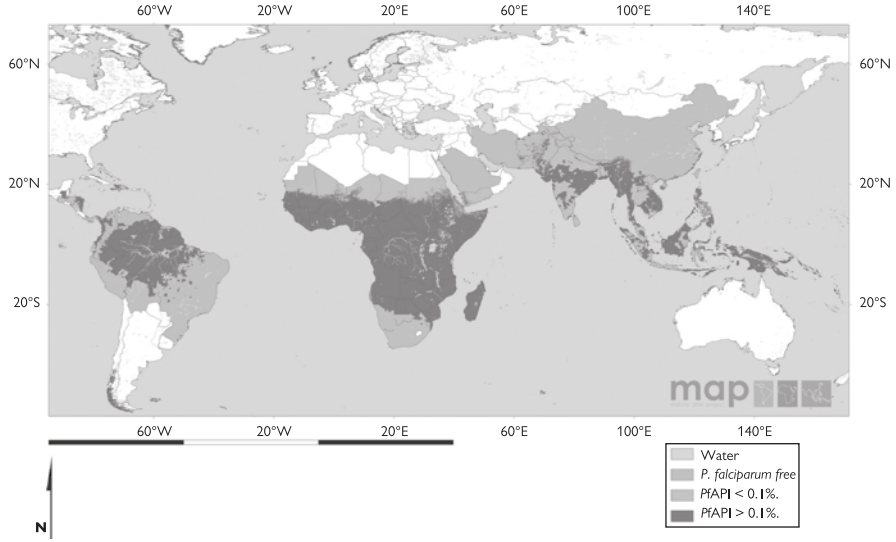


Fig. 2.2 The spatial limits of *Plasmodium falciparum* malaria transmission in 2010 (available at: http://www.map.ox.ac.uk/browse-resources/transmission-limits/Pf_limits/world/). *Pf*API, *P. falciparum* annual parasite incidence. Reproduced with permission from the Malaria Atlas Project (https://malariaatlas.org/). Licensed under Creative Commons Attribution 3.0 Unported License.

HIV infection

There is a complex interaction between HIV and malaria. Malaria ↑ viral loads in HIV+ve individuals, and HIV ↑ both the incidence of malaria (in areas of stable transmission) and the occurrence of severe malaria complications (in areas of unstable transmission; Box 2.1). In pregnancy, HIV predisposes the mother to malaria and the newborn to congenital malaria. HIV also exacerbates the low birth weight associated with malaria in pregnancy.

Box 2.1 Complications of malaria

Falciparum malaria

- Falciparum malaria may → severe disease and death (➲ Severe malaria, p. XX).
- In endemic areas where parasites persist after treatment or patients are soon reinfected, anaemia is common.
- In some countries, 30% of patients with falciparum malaria develop symptomatic *P. vivax* infection within 2mths without re-exposure to parasites, implying an initial mixed infection or activation of existing hypnozoites in the liver.
- Hyperreactive malarial splenomegaly syndrome presents with massive splenomegaly (Box 2.2).

The benign malarias

- *P. vivax*: recent reports suggest benign is a misnomer as infection may → a higher mortality than previously recognized.
- *P. vivax*: a rare complication is splenic rupture (mortality 80%). It results from acute enlargement +/− trauma.
- *Relapses*: *P. vivax* and *P. ovale* may relapse from 30d to 5yrs after 1° infection despite treatment that eliminates all blood forms, due to latent liver hypnozoites undergoing schizogony and re-entering the bloodstream.
- *P. malariae*: persistent parasites may cause recurrent fevers when infection recrudesces, even decades after 1° infection. Fevers ↓ in frequency and severity over time. Anaemia and splenomegaly may occur.
- *P malariae*: chronic infection may be associated with nephrotic syndrome (Box 2.2).

Clinical features

P. falciparum infection, if treated correctly, generally follows a relatively uneventful course. However, without effective therapy it can rapidly become life-threatening, esp. in young children and non-immune adults.

P. ovale, *P. malaria*, and *P. vivax* infection are much less likely to → severe disease or death. Reports from Southeast Asia indicate that *P. vivax* may be less benign than previously thought. Chronic infection or infection of pregnant women with these 'benign' species may → marked morbidity, e.g. anaemia and ↓ birth weight.

Two important features distinguish falciparum infection from the other malarias and account for the differences in severity:

- Only *P. falciparum* malaria → high blood parasite densities.
- Only *P. falciparum* demonstrates 'sequestration' in the microvasculature of RBCs containing mature parasites.

Sequestration results mainly from cytoadherence of parasitized RBCs to endothelial cells in the postcapillary venules of critical organs including the brain, although other factors, such as ↓ deformability of both parasitized and unparasitized RBCs, autoagglutination of parasitized cells, and adherence of unparasitized to parasitized RBCs (rosetting) may play a role.

Acute malaria

The clinical presentation of acute malaria in non-immune adults with rigors is well known. There is usually a history of travel to, or residence in, an endemic area. Even the best compliance with the most effective antimalarial chemoprophylaxis cannot exclude malaria. There may be a prodrome of tiredness and aching. The features of a classical paroxysm are:

- An abrupt onset of an initial 'cold stage' associated with a dramatic rigor (paroxysm) in which the patient visibly shakes.
- An ensuing 'hot stage' during which the patient may have a temperature >40°C, be restless and excitable, and vomit.
- Finally, the sweating stage, during which the patient's temperature ↓ to normal (defervesces) and sleep may ensue.

Such a paroxysm can last 6–10h; a prolonged asymptomatic period may follow lasting 38–42h in the case of vivax and ovale malaria ('tertian' fever) and 62–66h in *P. malariae* infections ('quartan' fever; see Box 2.2).

In falciparum malaria, the periodicity of fever is less predictable and the fever may be continuous. There may be an accompanying headache, cough, myalgia (flu-like symptoms), diarrhoea, and mild jaundice.

Malaria rarely, if ever, causes lymphadenopathy, pharyngitis, or a rash, and alternative diagnoses need to be considered for these symptoms. In children, the presentation is usually a non-specific fever with any of a range of symptoms incl. cough, diarrhoea and vomiting, anaemia, and hypoglycaemia. Jaundice, pulmonary oedema, and renal failure are rarer in children than adults, although progression to other severe complications is usually faster (1–2d) in children.

Box 2.2 Chronic malaria

The persistence of low-level parasitaemia in the blood may → 'chronic' malaria. Symptoms include recurrent acute attacks of malaria, anaemia, hepatosplenomegaly, diarrhoea, ↓ weight, and ↓ incidence of other infections. Chronic malaria may resolve, with the onset of partial immunity, or progress, with 2° complications.

Hyperreactive malarial splenomegaly

Formerly called tropical splenomegaly syndrome. May follow recurrent infections. It is characterized by massive splenomegaly, profound anaemia, 2° bacterial infections, fever, and (occasionally) jaundice. There is hypersplenism with pancytopenia, hypergammaglobulinaemia, and a lymphocytic infiltrate in the liver. There is ↑↑ serum immunoglobulin M (IgM). Although malarial parasites are seldom found in the blood, the condition responds to prolonged courses of antimalarial drugs.

Burkitt's lymphoma

A childhood tumour common in areas of high falciparum malaria transmission. It is thought to be due to Epstein–Barr virus (EBV) infection in the setting of ↓ T-cell immunity associated with repeated malaria infections (➲ Infectious mononucleosis, p. 737, and Burkitt's lymphoma, p. 472).

Quartan malarial nephropathy

P. malariae infection appears to cause nephrotic syndrome, particularly in tropical Africa. Malarial antigens are found in the renal glomerular basement membrane. Unfortunately, the condition does not respond to antimalarial treatment, glucocorticoids, or cytotoxic drugs, but is becoming less common.

Pregnancy

Pregnancy ↑ risk from falciparum malaria in all levels of endemicity.

- In areas of high, stable transmission, despite higher parasite burdens, many infections are asymptomatic (though often anaemic), but result in ↓ birth weight, with consequent ↑ infant morbidity and mortality. The effect is greater in primigravidae.
- In areas of unstable transmission, pregnancy → more severe malaria, particularly anaemia, hypoglycaemia, and acute pulmonary oedema. Fetal distress, premature labour, and stillbirth occur and low birth weight is common. In severe malaria, fetal death is the usual outcome.
- *P. vivax* malaria in pregnancy is also associated with ↓ birth weight, although to a lesser extent than *P. falciparum*.
- Congenital malaria has a very variable incidence. In some high-transmission areas, parasitaemia in the newborn is >50%, but symptomatic disease rare.

Severe malaria

Severe malaria is a serious multisystem disease. The onset can be rapid, with death (particularly in children) occurring in hours. In travellers from endemic regions, it is common when the diagnosis is made late and malaria treatment delayed (Box 2.3).

Cerebral malaria

This is the most important complication of falciparum malaria; it is uniformly fatal if untreated and has a 10–20% treated mortality. It most often occurs in non-immune adults and in children. Cerebral malaria (CM) is 'unrousable coma in the presence of peripheral parasitaemia where other causes of encephalopathy have been excluded'. However, any alteration in consciousness in the context of falciparum malaria should be taken seriously. Neck rigidity and photophobia are not usually seen and Kernig's sign is −ve. There may be one or more of diffuse cerebral dysfunction with coma, generalized convulsions (~50%), focal neurological signs, and brainstem signs such as abnormal doll's eye or oculovestibular reflexes. Retinal haemorrhages are seen in ~15% of cases, ↑ to ~40% if pupillary dilatation and indirect ophthalmoscopy are used. A distinct pattern of whitening indicates cerebral sequestration in fatal cases in children. Neurological sequelae are found in ~5% of survivors (10% in children) and include hemiparesis, cerebellar ataxia, cortical blindness, hypotonia, and cognitive impairment. In children, CM carries 10–40% mortality, with most deaths within the first 24h.

Reduced Glasgow Coma Scale (GCS) score can also be caused by hypoglycaemia, which must be excluded. In children, multiple convulsions are a common presentation of malaria and do not necessarily imply CM. Malarial convulsions can occur at any temperature and post-ictal coma may be prolonged. In deep coma, abnormalities of posture and muscle tone are frequently seen. For young children, use the Blantyre Coma Scale (BCS; see Box 9.3) to grade the coma.

Respiratory distress

This is seen as rapid, laboured breathing, sometimes with abnormal rhythms of respiration. In children, there may be intercostal recession, use of the accessory muscles of respiration, and nasal flaring, which is difficult to differentiate from an acute respiratory infection. Respiratory distress in patients with malaria can result from a number of pathologies; each requires different treatment:

- In most cases, particularly in children, respiratory distress represents respiratory compensation for a profound metabolic acidosis. Severe metabolic acidosis (base deficit >12mmol/L) is associated with an 8-fold ↑ risk of death in children.
- Acute respiratory distress syndrome (ARDS) caused by direct alveolar capillary damage by parasites and neutrophils; worsened by hypoalbuminaemia and iatrogenic fluid overload (rare in children).
- A respiratory infection because of immunosuppression caused by malaria.
- Air hunger as a result of severe anaemia.

Box 2.3 WHO criteria for severe malaria

One or more of the following:

Clinical features of severe malaria

- ↓ consciousness (including unrousable coma).
- Prostration, i.e. generalized weakness so that the patient cannot sit, stand, or walk without assistance.
- Multiple convulsions: >2 episodes within 24h.
- Deep breathing and respiratory distress (acidotic breathing).
- Acute pulmonary oedema and ARDS.
- Circulatory collapse or shock, systolic BP <80mmHg in adults and <50mmHg in children.
- Acute kidney injury (AKI).
- Clinical jaundice plus evidence of other vital organ dysfunction.
- Abnormal bleeding.

Laboratory and other tests

- Hypoglycaemia (<2.2mmol/L or <40mg/dL).
- Metabolic acidosis (plasma bicarbonate <15mmol/L).
- Severe normocytic anaemia (children: haemoglobin (Hb) <5g/dL, packed cell volume (PCV) <15%; adults: Hb <7g/dL, PCV <20%).
- Haemoglobinuria.
- Hyperparasitaemia (varies with transmission, 2% low to 20% high).
- Hyperlactataemia (lactate >5mmol/L).
- Renal impairment (serum creatinine (Cr) >265μmol/L).
- Pulmonary oedema (radiological).

Adapted from World Health Organization Guidelines for Malaria February 2021

Anaemia

All patients with malaria will have some ↓ in Hb. The anaemia is normocytic. Severe anaemia with haematocrit <15% (or Hb <5g/dL) in the presence of parasitaemia >10,000/μL (about 0.2% of RBCs infected) is a common presentation in African children. Pallor, breathlessness, gallop rhythm, and respiratory distress are common features of severe anaemia. Anaemia is exacerbated by 2° bacterial infections, haemorrhage, and pregnancy. Hyperparasitaemia and/or G6PD deficiency can → massive intravascular haemolysis. In children, repeated episodes of otherwise uncomplicated malaria may → chronic normochromic anaemia with dyserythropoietic changes in the bone marrow.

Jaundice

Common in adult patients and results from several mechanisms:

- Haemolysis.
- Hepatocellular damage.
- Cholestasis.

Both unconjugated and conjugated bilirubin may be >50μmol/L (3.0mg/dL). Clinical signs of liver failure very rare unless concomitant viral hepatitis. Significant jaundice is rare in children.

Renal impairment

May be prerenal or renal in origin, usually occurs in adults, and is characterized by a ↑ serum Cr (>265μmol/L or 3mg/dL) and ↑ urea, with oliguria (<400mL urine/24h in an adult) or anuria due to acute tubular injury. Renal impairment may occur at the time of maximal parasitaemia or after the parasites have been cleared. In some cases, there is polyuria. Renal failure (anuria) in malaria has a poor prognosis (~45% die) unless acute dialysis or haemofiltration can be provided, in which case, good recovery of renal function is expected within 1–2wks.

Blackwater fever

Massive haemoglobinuria (urine becomes very dark, like Coca-Cola) during malaria. Urine is +ve for blood (Hb) on dipsticks, but no RBCs are seen on microscopy. Cause is not completely characterized, but in some cases it follows treatment with quinine, or treatment or prophylaxis with oxidant drugs, e.g. primaquine. More common in patients with G6PD deficiency or other RBC enzyme deficiencies (e.g. pyruvate kinase). Historically, blackwater fever was more common and mortality much higher.

Hypoglycaemia

Whole blood glucose (<2.2mmol/L, 40mg/dL) may be due to ↓ liver function or quinine/quinidine-induced hyperinsulinaemia (pregnant women are particularly prone). It presents with anxiety, sweating, breathlessness, dilated pupils, oliguria, hypothermia, tachycardia, and light-headedness, eventually → ↓ consciousness, convulsions, and coma. However, it can easily be missed in patients with disturbed conscious level, esp. children. In a fasting adult, hepatic glycogen stores last ~2d; in a child ~12h. Hence, hypoglycaemia is common in young children (especially those with CM, hyperparasitaemia, or convulsions). It is also more common in pregnant women. Hypoglycaemia indicates a poor prognosis and is a risk factor for neurological sequelae (Box 2.4).

Lactic acidosis

A pH <7.3, or ↑ plasma and CSF lactate levels (plasma >5mmol/L) and a low plasma HCO_3^- (<15mmol/L) carry a poor prognosis in both adults and children. Acidosis is a major contributor to respiratory distress, especially in children.

Fluid and electrolyte disturbances

Hypovolaemia and dehydration are thought to be common, although recently this has become controversial as fluid resuscitation may ↑ mortality (➲ p. 642). Low Na^+, Cl^-, PO_4^-, Ca^{2+}, Mg^{2+}, and endocrine dysfunction also occur, but seldom have major clinical implications except in the severely ill.

Acute respiratory distress syndrome

Common in non-immune adults but very rare in semi-immune children. Carries 50% mortality and may occur even when the patient is otherwise improving. Excessive IV fluid replacement ↑ this complication and is suggested by ↑ respiratory rate (exclude aspiration or acidosis). Predisposing causes incl. hyperparasitaemia, renal failure, and pregnancy (may occur suddenly after delivery). Hypoxia may → convulsions and death within a few hours.

Box 2.4 Indicators of a poor prognosis

Clinical

- Marked agitation.
- Hyperventilation (respiratory distress).
- Hypothermia (<36.5°C).
- Deep coma.
- Repeated convulsions.
- Bleeding.
- Anuria.
- Shock.

Laboratory

- Blood film showing hyperparasitaemia >100,000/μL (about 2% of cells infected) in low-transmission areas or >250,000/μL (about 5%) in high-transmission areas.
- Blood film showing >20% of parasites to be 'late stages' (pigment-containing trophozoites and schizonts).
- Blood film showing >5% of neutrophils with visible pigment.
- Hypoglycaemia (<2.2mmol/L).
- Hyperlactataemia (>5mmol/L).
- Acidosis (arterial pH <7.3, serum HCO_3 <15mmol/L).
- ↑ serum Cr (>265μmol/L).
- ↑ total bilirubin (>50μmol/L).
- Leukocytosis (>12,000/μL).
- Severe anaemia (PCV <15%).
- Coagulopathy:
  - ↓ platelet count (<50,000/μL).
  - ↑ prothrombin time (PT).
  - ↓ fibrinogen (<200mg/dL).

Shock (algid malaria)

- Cold, clammy cyanotic skin.
- Weak rapid pulses.
- Prolonged capillary refill time (>3s).
- Supine systolic BP <70mmHg (<50mmHg in children) suggests circulatory collapse.
- Shock in malaria is commonly associated with 2° bacterial infection, metabolic acidosis, pulmonary oedema, dehydration, or a gastrointestinal (GI) bleed.

Give empiric parenteral antibiotics for bacteraemia, e.g. IV ceftriaxone.

Disseminated intravascular coagulation

This is due to pathological activation of the coagulation cascade. Disseminated intravascular coagulation (DIC) may → bleeding gums, epistaxis, petechiae, haematemesis, and/or melaena with significant blood loss. DIC occurs in <10% of patients, but is commoner in non-immune people (esp. travellers). Blood film shows thrombocytopenia and schistocytes (damaged RBCs). There is ↑ PT and ↓ plasma fibrinogen (note that thrombocytopenia alone may be present in many cases of malaria and does not, by itself, indicate DIC).

Hyperparasitaemia

A parasite density >100,000 parasites/μL (~2% of RBCs infected) is associated with ↑ mortality though in highly endemic areas, individuals may tolerate greater densities without major clinical features. Parasitaemias of >500,000 parasites/μL (>10% RBCs infected) carries a 50% case fatality in non-immune individuals.

Gastrointestinal symptoms

Common in children. Nausea, vomiting, abdominal pain, and watery diarrhoea are frequently seen. Persistent vomiting requires urgent parenteral drug administration.

Secondary infection

In malaria, septicaemia, pneumonia (e.g. following aspiration), UTI (following catheterization), and postpartum sepsis are common. Gram −ve septicaemia may occur without any focus of infection and is common in semi-immune children, → presumptive antibiotic treatment in all cases of severe malaria in children.

Differential diagnosis

Box 2.5 Differential diagnosis of malaria

Malaria is a great mimic of several clinical presentations:

- Fever must be differentiated from common viral (e.g. influenza, Covid-19) and bacterial infections, as well as other endemic diseases, e.g. typhoid and rickettsial infections, viral illnesses, such as dengue fever and influenza, brucellosis, and respiratory and UTIs. Less common causes of tropical fevers include visceral leishmaniasis, trypanosomiasis, and relapsing fevers.
- Coma of CM must be differentiated from meningitis (incl. TB meningitis), encephalitis, enteric fevers, trypanosomiasis, brain abscess, and other causes of coma.
- Anaemia of malaria can be confused with other common causes of haemolytic anaemia in the tropics, e.g. haemoglobinopathies. Consider iron, folate, or vitamin B_{12} deficiency.
- Renal failure of malaria must be distinguished from massive intravascular haemolysis, sickle cell disease, leptospirosis, snake envenoming, use of traditional herbal medicines, glomerulonephritis, and renal disease of hypertension.
- Jaundice and hepatomegaly of malaria must be distinguished from viral hepatitis (A, B, and E; CMV and EBV), leptospirosis, yellow fever, biliary disease, and alcohol- or drug-induced liver disease.

Clinical diagnosis of malaria is notoriously inaccurate. A blood film or rapid diagnostic test (RDT) is essential (➲ Diagnosis, p. 51). Malaria cannot be diagnosed without a +ve blood film or RDT. However, in areas of stable transmission with high population parasite rates, a +ve test can be non-specific. In seriously ill patients, empiric antibiotic treatment should be given alongside antimalarial drugs.

Diagnosis

Wherever possible, a +ve diagnosis of malaria (or at least the presence of malaria parasites) should be made in all cases using either high-quality microscopy of peripheral blood film or, if unavailable, RDTs. Presumptive treatment without a diagnosis should be avoided wherever possible.

Even when using RDTs or blood smears, in high-transmission areas, where asymptomatic parasitaemia is common, overdiagnosis of malaria is a major problem. This can → undertreatment of the real cause of the symptoms, particularly when this is a bacterial infection. Cases of 'severe malaria' should routinely be treated with antibiotics, as well as antimalarials.

Nucleic acid detection tests using polymerase chain reaction (PCR) are extremely sensitive, highly accurate in speciation, and can be used to identify drug-resistant mutations. However, they are technologically complex and currently not used for routine diagnosis.

Blood films

See Colour Plates 1–4 and Fig. 2.3 for blood film diagrams and Fig. 2.4 for thick/thin film methodology. Thin films are basically peripheral blood smears; thick films are more sensitive since they enable examination of a larger quantity of blood per microscopic field, but require more expertise to read.

Maintain a high index of suspicion and study three blood films (or RDTs) if the fever does not resolve. Malaria infection may rarely occur via transfusion, needlestick injury, IV drug abuse, and during brief airport stopovers in endemic areas or when infected mosquitoes 'alight' from airplane flights from endemic areas and bite individuals ('airport' malaria). In falciparum malaria, the presence of schizonts in peripheral blood samples may indicate severe infection as these forms would normally sequester.

Pitfalls of blood films

- Expertise is required for preparation and accurate interpretation of blood films; this is often lacking in many settings.
- A single −ve film does not exclude malaria. Repeat on three occasions at intervals. Blood films do not have to be taken at times of fever spikes. The patient may have been partially treated, suppressing infection. Malaria prophylaxis should be stopped while investigating fever.
- In endemic areas, a +ve film does not prove that malaria is responsible for the current symptoms.
- Correlation between parasite density and disease severity can be poor. Patients with a low parasitaemia may be very ill, while semi-immunes may have high parasitaemias with relatively few symptoms.
- Platelets, cell fragments, and impurities in the stain can be mistaken for malarial parasites.

Staining Consult a laboratory manual for more details.

Giemsa stain

May be used for thick and thin films, but is costly and difficult to do. It should be filtered before use. Thin films must first be fixed in anhydrous methanol then dipped in 10% Giemsa for 20–30min; thick films are unfixed, stain with 5% solution for 30min.

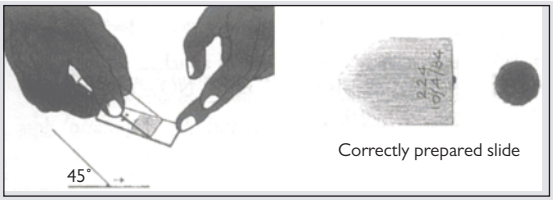


Fig. 2.3 Preparing a blood film.

- Clean the tip of the patient's index finger.
- Pierce the pulp of the fingertip with a sterile lancet or needle.
- Squeeze the finger until a droplet of blood forms and place it onto the middle of a clean slide (holding the slide by the edges). This is for the thin film.
- Place a further three droplets of blood onto the slide at a point to one side of the first droplet. These are for the thick film.
- Using a second clean slide as a spreader, touch the first, small drop with the edge and allow the blood to run along its edge. With the spreading slide at 45°, push the spreader forwards slowly, ensuring even contact, so that the blood is spread as a thin film over the surface of the slide (Fig. 2.3).
- Using the corner of the spreading slide, amalgamate three drops of blood on the other half of the slide into a single small, denser film about 1cm in diameter.
- Label the slide with a pencil and allow to dry horizontally.

Problems

Badly positioned blood droplets, too much/too little blood, a greasy slide, and a chipped edge of the spreader slide.

Field's stain

Uses two solutions, A and B, that are cheaper and suitable for rapid bulk staining. Thin films should be fixed in methanol, thick films are unfixed. For thick films, dip dried slides into solution A for 5s, avoiding agitation. Wash in tap water (preferably neutral pH) for 5s, avoiding washing unfixed smear off slide. Then dip into solution B for 3s. Wash again in water for 5s, then allow to dry vertically. The centre of the film may not be stained, but optimal parasite staining occurs at the edges of the film. For thin films, use solution B before solution A.

Rapid diagnostic tests

- Numerous antigen-capture RDTs use a monoclonal antibody to detect the histidine-rich protein II (HRP2) of *P. falciparum*. These require minimal training to perform. Their main limitations are that they are non-quantitative, their sensitivity is ↓ at low parasitaemias, and they cannot be used to monitor treatment response, as they remain +ve for some time after clearance of parasitaemia. There are some parasites that lack HRP2 and therefore are not detectable by this approach; this has been reported in Peru and Eritrea but may become more common, forcing a move to alternative diagnostic approaches.
- Other tests detect parasite lactate dehydrogenase (pLDH); or parasite aldolase. pLDH and aldolase are +ve in all malaria species (pan-specific).
- In some tests, HRP2 detection is combined with pan-LDH or pan-aldolase. Therefore, detection can diagnose all species with good sensitivity (>95%), and distinguish *P. falciparum* from non-falciparum malaria infections.

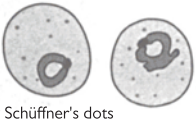
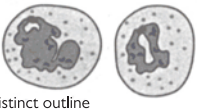
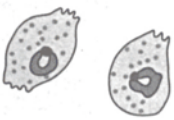
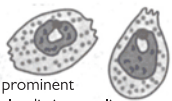
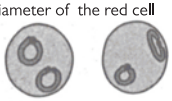
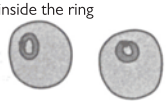
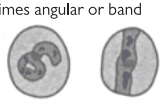
	Early trophozoite (ring form)	Mature trophozoite
Plasmodium vivax	Thick rings, ⅓–½ the diameter of the red cell  A few Schüffner's dots Accolé (shoulder) forms and double dots less common than with *P. falciparum*	Ameboid rings, ½–⅔ the diameter of the red cell Pale blue or lilac parasite with prominent central vacuole  Indistinct outline Scattered fine yellowish-brown pigment granules or rods
Plasmodium ovale	Thick, compact rings, ⅓–½ the diameter of the red cell  Numerous Schüffner's dots but paler than with *P. vivax*	Thick rings, less irregular than those of *P. vivax*, ⅓–½ the diameter of the red cell  Less prominent vacuole, distinct outline. Yellowish brown pigment which is coarser and darker than that of *P. vivax* Schüffner's dots prominent
Plasmodium falciparum	Delicate rings, ⅛–¼ the diameter of the red cell  Double dots and Accolé forms common	Fairly delicate rings, ⅓–½ the diameter of the red cell  Red-mauve stippling (Maurer's dots or clefts) may be present Mature trophozoites are less often present in peripheral blood than ring forms
Plasmodium malariae	Small, thick, compact rings Small chromatin dot which may be inside the ring  Double dots and Accolé forms rare	Amoeboid form more compact than *P. vivax* Sometimes angular or band forms  Heavy, dark-yellow-brown pigment No stippling unless overstained

Fig. 2.4 Diagrams of malarial blood cells.

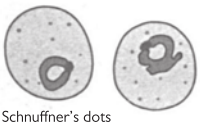
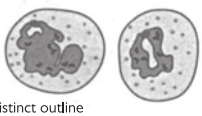
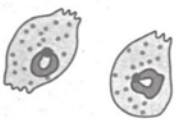
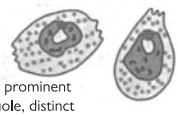
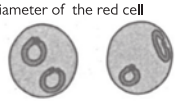
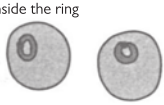
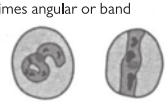
	Early trophozoite (ring form)	Mature trophozoite
Plasmodium vivax	Thick rings, ⅓–½ the diameter of the red cell  A few Schnuffner's dots Accolé (Shoulder) forms and double dots less common than with *P. falciparum*	Ameboid rings, ½–⅔ the diameter of the red cell Pale blue or lilac parasite with prominent central valuole  Indistinct outline Scattered fine yellowish-brown pigment granules or rods
Plasmodium ovale	Thick, compact rings, ⅓–½ the diameter of the red cell  Numerous Schuffner's dots but paler than with *P. vivax*	Thick rings, less irregular than those of *P. vivax*, ⅓–½ the diameter of the red cell  Less prominent vacuole, distinct outline Yellowish brown pigment which is coarser and darker than that of *P. vivax* Schuffner's dots prominent
Plasmodium falciparum	Delicate rings, ¼–¼ the diameter of the red cell  Double dots and Accolé forms common	Fairly delicate rings, ⅓–½ the diameter of the red cell  Red-mauve stippling (Maurer's dots or clefts) may be present Mature trophozoites are less often present in peripheral blood than ring forms
Plasmodium malariae	Small, thick, compact rings Small chromatin dot which may be inside the ring  Double dots and Accolé forms rare	Ameboid form more compact than *P. vivax* Sometimes angular or band forms  Heavy, dark-yellow-brown pigment No stippling unless ovestained

Fig. 2.4 *(Continued)*.

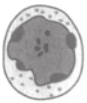
	Early schizont	Late schizont
Plasmodium vivax	Rounded or irregular Amoeboid Loose central mass of fine yellowish-brown pigment  Schizont almost fills cell Schüffner's dots	12–24 (usually 16–24) medium-sized merozoites 1–2 clumps of peripheral pigment  Schizont almost fills cell Schüffner's dots
Plasmodium ovale	Round, compact Darkish brown pigment, heavier and coarser than that of *P. vivax*  Schüffner's dots	6–12 (usually 8) large merozoites arranged irregularly like a bunch of grapes  Central pigment Schüffner's dots
Plasmodium falciparum	Not usually seen in blood Very small, amoeboid Scattered light-brown to black pigment	Not usually seen in blood 8–32 (usually few) very small merozoites; grouped irregularly Peripheral clump of coarse dark brown pigment
Plasmodium malariae	Compact, round, fills red cell  Coarse dark yellow-brown pigment	6–12 (usually 8–10) large merozoites, arranged symmetrically, often in a rosette or daisy head formation  Central coarse dark yellowish-brown pigment

Fig. 2.4 *(Continued)*. Reproduced with permission from Bain, Barbara J., *Blood Cells: A Practical Guide* (5th edn, Oxford, 2015) © 2015, John Wiley and Sons.

General management

Once a diagnosis of malaria is made with laboratory support, assess the patient for the presence of features of severe malaria (➔ Severe malaria, p. 43). If a laboratory diagnosis cannot be made quickly or is not available, patients with suspected severe malaria should be treated empirically without delay.

Basic rules

- In many instances, especially in endemic areas, uncomplicated malaria patients can be treated as outpatients.
- Advise patients to return promptly if symptoms worsen or do not improve within 48h.
- Beware of sending home patients who have mild symptoms, but high levels of parasitaemia, since they may deteriorate rapidly.

All patients will require antimalarial chemotherapy

Antimalarial treatment with appropriate antimalarial drugs should be started immediately, usually following national guidelines (Box 2.7). Choose parenteral therapy in severely ill patients or those unable to tolerate oral medication.

Many patients will need analgesics

If fever causes distress, an analgesic/antipyretic should be given orally or by suppository. Paracetamol has been shown to prolong parasite clearance, although the clinical significance of this is unclear. Several studies demonstrated a greater antipyretic effect with ibuprofen, which should be considered if there are no contraindications. Avoid aspirin in children because of Reye's syndrome, because platelets may be low, and because aspirin can ↑ acidosis.

Management

- *Assess the airway, breathing, and circulation*: intervene where necessary. Record vital signs: temperature, pulse, BP, respiratory rate and capillary refill time.
- *Obtain reliable venous access*: take blood for investigations incl. blood film, Hb or haematocrit, blood glucose, blood group, and crossmatch. If available, do blood culture, biochemistry (electrolytes, renal and liver function), arterial blood gases (ABG) analysis (if any signs of severe disease), and coagulation studies.
- *Treat hypoglycaemia (blood glucose <2.2mmol/L) if present*: give 20% glucose 50mL, retest and repeat if necessary. 50% solutions have been used, but these should be given very carefully if there is a risk of extravasation. In children, give 10% glucose at 5mL/kg by slow IV bolus. Follow bolus treatment with 10% glucose infusion (0.1mL/kg/h). Monitor blood glucose levels frequently, especially following quinine infusion.
- *Weigh patient and initiate antimalarial therapy*: see ➔ Antimalarial chemotherapy, p. 58.

Box 2.6 *WHO Guidelines for the Treatment of Malaria*, 3rd edn, 2015

The WHO guidelines encompass all the recent important developments in the treatment of malaria, both uncomplicated and severe. The guidelines are evidence based, a valuable resource on all aspects of treatment, and discuss in detail two major points:

- The wide acceptance and recommendation of artemisinin-based combination therapy (ACT) as treatment of choice for uncomplicated falciparum malaria. The main clinical advantages of ACTs are a rapid therapeutic response and rapid initial ↓ in parasite numbers; in addition, they ↓ the chance of drug resistance emerging and spreading and may, through their gametocytocidal effect, ↓ transmission.
- The recommendation that artesunate, the most rapidly acting parenteral antimalarial, is the drug of choice for patients with severe malaria—including infants, pregnant women in all trimesters and lactating women.

Complete guidelines from WHO 🔊: http://www.who.int/malaria/publications/atoz/9789241549127/en/.

- *Consider empirical broad-spectrum antibiotic therapy*: e.g. IV ceftriaxone if hypotensive or suspicion of bacterial infection (in Kenya, bacteraemia occurs in ~10% of children with severe malaria).
- *Lumbar puncture (LP)*: patients with ↓ levels of consciousness should have a LP to exclude bacterial meningitis. In CM (Box 2.8) the CSF is normal. If there is concern about ↑ ICP, if the patient is too unwell for the procedure, or if platelets count too low, LP can be delayed, but antibiotic cover should be given.
- *Assess hydration*: consider urinary catheterization. Rehydration may be required, particularly if diarrhoea and vomiting are present. Adults with severe falciparum malaria usually require 1–3L of isotonic saline over the first 24h. However, avoid overhydration. In children, rapid fluid resuscitation may be →↑ mortality, see notes of use of fluids in the sick child, ➲ Treatment of shock, p. 6.
- *Monitor renal output and BP hourly*: aim to keep central venous pressure (if available) in the low–normal range.
- *Blood transfusion* with pathogen-free, compatible fresh blood or packed cells should be considered in patients with a haematocrit level <15% or Hb <5g/dL. Transfusion should be given urgently in children with Hb <4g/dL or Hb <5g/dL with respiratory distress or acidosis or parasitaemia >10%; in such cases, give blood 10mL/kg over 30min, then a further 10mL/kg over 2–3h without diuretics. In DIC, fresh blood, clotting factors (fresh frozen plasma (FFP)), and/or platelets should be given as required.
- *Exchange transfusion*: has not been subject to a RCT. It has been rarely carried out since the use of artesunate, with its rapid and reliable action, became established.
- *Dialysis if patient develops renal failure*: haemofiltration or haemodialysis may be indicated. Peritoneal dialysis should be used if these are unavailable but is less effective.

- *Oxygen and mechanical ventilation*: may be required for patients with respiratory distress or significantly ↑ ICP. If distress is due to pulmonary oedema, the patient should be nursed at 45° and IV diuretics given. Haemofiltration may be used if available.
- *Inotropes*: e.g. dopamine may be given, preferably through a central line, if hypotension does not respond to volume expansion. Adrenaline should be avoided as it can ↑ acidosis.

Box 2.7 Cerebral malaria

Treat as in ➲ General management, p. 55, with the following additional specific measures:

- Nurse the patient on their side to avoid aspiration of vomit. Turn every 2h.
- The patient should be catheterized and have temperature, heart rate, RR, BP, and fluid balance measured regularly.
- Consciousness must be assessed regularly with the GCS or BCS (➲ p. Boxes 9.2 and 9.3, p. 387).
- Hypoglycaemia must be treated promptly, but is very difficult to detect in an unconscious patient. Blood sugar should be actively monitored at least 4–6hrly and whenever there is any deterioration in the patient's clinical condition.
- *If convulsions arise*: be alert, since they may be subtle. Treat with diazepam (10mg in adults) by slow IV, repeat once if necessary. An alternative is diazepam 10–20mg rectally, repeated after 10–15min if required.
- Corticosteroids, mannitol, or other ancillary agents for cerebral oedema are of no proven benefit.

Antimalarial chemotherapy

ACTs are now established as the standard for treatment of uncomplicated falciparum malaria (Box 2.9) and parenteral artesunate is the drug of choice for severe malaria. Resistance to many antimalarial drugs is an ↑ problem worldwide and it is important to have up-to-date information on local resistance patterns. Chloroquine, for example, can no longer be used to treat falciparum malaria in most parts of the world. Resistance to the artemisinin derivatives has been described in Southeast Asia and, resistance to partner drugs in the ACT combinations is significant in many areas.

Artemisinin-based combination therapies

ACT uses two or more drugs with independent modes of action. The aim of combinations is to ↓ the spread of resistance, with the two components protecting each other. This principle has been widely applied in the treatment of HIV and TB. In ACTs, one of these agents is an artemisinin derivative, the most rapidly acting class of antimalarial. This ensures rapid ↓ parasitaemia, which ↓ risk of developing resistance. Artemisinin derivatives are also gametocytocidal and thus may ↓ malaria transmission. Partial courses of ACTs should not be given (even in patients who are considered to be semi-immune or the diagnosis is uncertain) as this may → development of resistance. For non-artemisinin-based treatment, see comments in ➲ Box 2.9, p. 61.

Treatment of uncomplicated *P. falciparum* malaria

- The aim is to ↓ parasitaemia as quickly as possible and to prevent recrudescence of the infection. Antimalarial drugs are given orally if tolerated. If the species is unknown or there is mixed infection, treat as falciparum malaria.
- ACTs are the recommended treatment of choice for uncomplicated falciparum malaria worldwide. Monotherapy is specifically discouraged.
- Be aware of local patterns of resistance, particularly to the artemisinin derivative partner drug. These will influence the first-line ACT for the area.
- Treatment failures within 14d of receiving an ACT should be treated with a second-line antimalarial (➲ Currently recommended ACTs, p. 61) (Box 2.10).
- Treatment failures (recurrent parasitaemia) after 14d can be retreated with the original first-line ACT. However, retreatment with mefloquine within 28d is associated with an ↑ risk of neuropsychiatric disorder, so if the first-line ACT was artesunate + mefloquine, a second-line antimalarial should be given.

Currently recommended ACTs

Artemether + lumefantrine

Fixed-dose combination (artemether 20mg/lumefantrine 120mg in each tablet). Six doses over 3d. Should be taken with milk or fat-containing food. For older children and adults, tablets containing 40mg artemether and 240mg lumefantrine are also available; if using these halve the number of tablets listed here:

Box 2.8 Treatment of the 'benign' malarias

- The standard treatment is chloroquine 25mg base/kg divided over 3d (e.g. 10mg base/kg followed by 5mg base/kg at 6h, 24h, and 48h). ACTs can be used.
- *P. malariae* does not produce hypnozoite forms, so chloroquine is curative.
- Hypnozoite stages of *P. ovale* and *P. vivax* are not affected by blood schizonticides, such as chloroquine, so to prevent relapses and effect a 'radical cure', primaquine (a liver schizonticide) must be given as well (0.25mg base/kg daily for 14d (0.375–0.5mg base/kg daily in Southeast Asia and Oceania, where relatively primaquine-resistant strains occur)). Primaquine can → GI symptoms; it should be given with food.
- Primaquine is an oxidant → haemolysis in G6PD-deficient individuals. Screening is generally unavailable, but in areas where mild to moderate G6PD deficiency is the common variant, primaquine in weekly doses of 0.75mg base/kg for 8wks is better tolerated. Primaquine should not be given in severe G6PD deficiency. It should also not be given to pregnant women.
- Chloroquine-resistant *P. vivax* is increasingly a problem (particularly in Oceania, Indonesia, and Peru), and can be treated with an ACT combined with primaquine.
- The benign malarias are susceptible to all ACTs (the exception being *P. vivax* and artesunate + sulfadoxine–pyrimethamine (SP), since *P. vivax* responds poorly to SP in many areas). Primaquine is still required for radical cure.

Adult dose Weight >35kg: four tablets at 0, 8, 24, 36, 48, and 60h.

Paediatric dose

Weight 25–34kg: three tablets/dose; 15–24kg: two per dose; 5–14kg: one per dose. This is the equivalent of 1.7/12mg/kg body weight of artemether and lumefantrine, respectively, per dose, given bd for 3d, with a therapeutic dose range of 1.4–4mg/kg of artemether and 10–16mg/kg of lumefantrine.

Artesunate + mefloquine

Suitable for use in areas of multidrug resistance (Southeast Asia); effective elsewhere, but expensive. Available as a fixed-dose formulation of paediatric tablets containing 25mg artesunate and 55mg mefloquine hydrochloride (equivalent to 50mg mefloquine base) and adult tablets containing 100mg artesunate and 220mg mefloquine hydrochloride (equivalent to 200mg mefloquine base).

Dose

5 to <9kg: 25mg artesunate + 55mg mefloquine; 9 to <18kg: 50mg artesunate + 110mg mefloquine; 18 to <30kg: 100mg artesunate + 220mg mefloquine; ≥30kg 200mg artesunate + 440mg mefloquine. Target doses (ranges) of 4 (2–10) mg/kg body weight/d artesunate and 8.3 (5–11) mg/kg body weight/d mefloquine, given once a day for 3d.

Artesunate + sulfadoxine–pyrimethamine

Currently available as separate scored artesunate (50mg) and SP (500/25mg) tablets. Only suitable for areas where SP monotherapy 28d cure rates >80%. Useful in some parts of Africa, but these are diminishing rapidly.

Dose

A target of 4mg/kg/d artesunate given od for 3d and a single administration of 25/1.25mg/kg SP on day 1, with a therapeutic dose range between 2–10mg/kg/d artesunate and 25–70/1.25–3.5mg/kg SP.

Artesunate + amodiaquine

Now available as a fixed-dose combination (three tablet sizes containing artesunate/amodiaquine 100/270, 50/135, and 25/67.5mg). Only suitable for areas where amodiaquine monotherapy 28d cure rates exceed 80% (mainly West Africa).

Dose

A target of 4mg/kg/d artesunate and 10mg/kg/d amodiaquine od for 3d, with a therapeutic dose range between 2–10mg/kg/d artesunate and 7.5–15mg/kg/dose amodiaquine.

Dihydroartemisinin + piperaquine

Currently available as a fixed-dose combination in tablets containing 40mg dihydroartemisinin (DHA) and 320mg piperaquine (P) and paediatric tablets contain 20mg DHA and 160mg P.

Dose

Administered once a day for 3d, dose varying with body weight; 5 to <8kg: 20mg DHA + 160mg P; 8 to <11kg: 30mg DHA + 240mg P; 11 to <17kg: 40mg DHA + 320mg P; 17 to <25kg: 60mg DHA + 480mg Pl 25 to <36kg: 80mg DHA + 620mg P; 36 to <60kg: 120mg DHA +960mg P; 60 <80kg: 160mg DHA + 1280mg Pl >80kg: 200mg DHA + 1600mg P.

Artesunate + tetracycline or doxycycline or clindamycin

There are no blister co-packaged forms of any of these combination options. They are reserved for rare treatment failures to recommended ACTs and some special groups, e.g. artesunate/clindamycin in pregnant women failing ACT treatment (Box 2.12). Should only be used in a hospital setting.

Dose

Artesunate (2mg/kg od) plus tetracycline (4mg/kg qds) or doxycycline (3.5mg/kg od) or clindamycin (10mg/kg bd). These combinations should be given for 7d.

Reducing the transmissibility of treated *P. falciparum* infections

In low-transmission areas WHO recommends a single dose of 0.25mg/kg body weight primaquine with ACT to patients with P. falciparum malaria (except pregnant women, infants aged <6mths and women breastfeeding infants aged <6mths) to ↓ transmission. Testing for G6PD deficiency is not required.

Box 2.9 Non-artemisinin-based combination therapies

SP + chloroquine is not recommended, as resistance to both components is already widespread and no synergy has been demonstrated.

SP + amodiaquine in areas of parasite sensitivity may be more effective than either drug alone but less rapidly acting than ACTs. Only recommended when ACTs are unavailable.

Atovaquone + proguanil has been used to treat uncomplicated malaria in areas of artemisinin-resistant malaria, but this use is controversial because of the high risk of the development of resistance.

Box 2.10 Second-line antimalarials for falciparum malaria

Used in cases of treatment failure <14d after receiving an ACT.

In order of preference they are:

- An alternative ACT known to be effective in the region (generally a 3d course).
- Artesunate (2mg/kg od) plus either tetracycline (4mg/kg qds) or doxycycline (3.5mg/kg od) or clindamycin (10mg/kg bd).
- Quinine (10mg salt/kg tds) plus either tetracycline (4mg/kg qds) or doxycycline (3.5mg/kg od) or clindamycin (10mg/kg bd).

Regimens 2 and 3 should be given for 7d. The quinine regimens are poorly tolerated and adherence is often poor. Doxycycline and tetracycline should not be used in pregnancy or in children <8yrs.

Box 2.11 Pregnant and lactating women

- 1st trimester: quinine and clindamycin (see doses in ➲ Currently recommended ACTs, p. 58) given for 7d. If clindamycin is unavailable, give quinine monotherapy. Treatment failures should be treated with 7d of artesunate + clindamycin (➲ Currently recommended ACTs, p. 58). Use an ACT as first-line treatment if it is the only effective treatment available.
- 2nd and 3rd trimesters: an ACT that is known to be effective in the region, or artesunate + clindamycin (7d) or quinine + clindamycin (7d).
- Lactation: lactating women should in general be given standard antimalarial treatment, including ACTs, but should not receive dapsone, primaquine, or doxycycline/tetracycline.

Treatment of severe malaria

General management of the severely ill patient and of complications are covered in ➲ General management, p. 55. Severe malaria is a medical emergency. Full doses of parenteral antimalarial therapy should be started immediately and continued until the patient is well enough to take oral follow-on treatment.

Drugs currently in use

Artesunate

2.4mg/kg IV or IM at 0, 12, and 24h, then od. Artesunate is recommended for the treatment of severe malaria in all settings in patients above 20kg, incl. pregnant and lactating women.

Children weighing <20kg should receive a higher dose of artesunate (3mg/kg body weight per dose) to ensure equivalent exposure to the drug.

Artemether

IM injection into the anterior thigh, 3.2mg/kg then 1.6mg/kg/d. Artemether absorption from IM injection is erratic, especially in very ill patients. It is a recommended therapy if artesunate is unavailable.

Quinine

This is no longer recommended by WHO as first-line treatment for severe malaria, unless artesunate and artemether are unavailable. A loading dose of 20mg quinine salt/kg should be given on admission, then 10mg quinine salt/kg tds thereafter, each dose given by rate-controlled IV infusion over 4h or by divided IM injection (rate should *not* exceed 5mg/kg/h).

- For IV infusion, quinine must be diluted in 5–10mL/kg body weight of glucose or saline solution. For IM use, quinine should be diluted in normal saline to 60mg/mL and half the dose given in each anterior thigh. IM injection can cause abscess formation.
- Quinine can cause severe hyperinsulinaemic hypoglycaemia, particularly in pregnant women.
- In AKI or hepatic dysfunction, the dose should be reduced by one-third after 48h to prevent accumulation and resulting toxicity. Dose adjustment in renal failure is unnecessary if the patient is receiving haemofiltration or haemodialysis.
- The first dose can be reduced to 10mg salt/kg if there is certainty that the patient has received adequate pre-treatment with quinine before presentation. If in doubt, give the loading dose.

Quinidine

If the other, recommended, parenteral antimalarials are unavailable (e.g. in the USA), the antiarrhythmic drug quinidine (an enantiomer of quinine) may be used. Give 15mg base/kg infused IV over 4h, followed by 7.5mg base/kg over 4h every 8h. Cardiac monitoring is required. Dose adjustments are necessary in renal failure and hepatic impairment as for quinine. Convert to oral therapy as soon as possible.

Follow-on treatment

Following initial parenteral therapy, when the patient is well enough to take oral medication, a full course of an ACT known to be effective in the region should be given.

Box 2.12 Pre-referral treatment

Rectal artesunate is well absorbed and is an option to start treatment and prevent progression of severe disease while referral to a healthcare facility capable of giving parenteral treatment is made. Quinine can also be given intrarectally in such circumstances.

Box 2.13 Artemisinin resistance

Resistance to the artemisinin drugs has been described in Southeast Asia. This was seen initially in Western Cambodia, but is now also a problem on the Thailand–Myanmar border. Artemisinin resistance is characterized by prolonged parasite clearance and an ↑ in treatment failures. It is regarded as the single biggest global threat to malaria control and elimination programmes. See http://www.wwarn.org/resistance/malaria and http://www.who.int/malaria/areas/drug_resistance/updates/en/index.html for the latest information.

Prevention

Prevention against malaria includes both chemoprophylaxis and measures taken to ↓ the number of mosquito bites. Insect repellents containing diethyltoluamide (DEET) (10–50%) or picaridin (7%) should be used, and insecticide-treated bed nets in areas where anopheline mosquitoes bite indoors at night. Individuals should be aware of malarial symptoms, which may be non-specific, and report early for a blood film or RDT if malaria is suspected. Malaria vaccines are currently undergoing large-scale pilot implementation in Ghana, Malawi, and Kenya and may offer protection in the future (➲ Box 2.14, p. 67).

Travellers to malarial areas

Travellers should preferably begin prophylaxis 1wk (2–3wks in case of mefloquine) before arrival, and must continue for 4wks after departure, except in cases of atovaquone–proguanil and primaquine, where prophylaxis may be commenced 1d before entry into malarial area and end 7d after return.

Any febrile illness occurring <1yr of travel could be malaria. For long-term, non-immune residents, there is a balance between the risks of infection and side effects of chemoprophylaxis. It may be possible to target prophylaxis during the transmission season alone.

Malaria endemic areas

Antimalarial prophylaxis is not logistically or financially feasible for the entire population. It has been used in those at highest risk—young children and pregnant women—in endemic areas. Intermittent preventive treatment which may work at least partly through its prophylactic effects is recommended by the WHO for pregnant women living in Africa. Recently, seasonal malaria chemoprevention (SMC), given over a few months to children up to 5yrs, has been shown to markedly reduce childhood mortality in areas of the Sahel where malaria transmission occurs over a very restricted time period.

Drugs used in prophylaxis

Atovaquone–proguanil, mefloquine, doxycycline, and primaquine can all be used as prophylaxis throughout the malaria endemic world, whereas the usefulness of chloroquine and proguanil has been severely restricted by resistance.

Atovaquone–proguanil

Well-tolerated, once-daily, fixed-dose combination effective against all types of malaria, including multidrug-resistant falciparum malaria. Should be taken with food and a milky drink to improve absorption. There is insufficient data to recommend its use in pregnancy, and it is very expensive. Dose in children best adjusted to weight.

Dose Adult daily dose atovaquone 250mg/proguanil 100mg.

Mefloquine

Nausea, dizziness, and vivid dreams are common side effects, and approximately 1 in 10,000 recipients develops an acute reversible neuropsychiatric reaction. Mefloquine is not recommended in neonates, but has been used for prophylaxis in pregnancy.

Dose

250mg oral weekly in adults and children >45kg (62.5mg weekly in children 6–16kg; 125mg for 16–25kg; 187.5mg for 25–45kg).

Doxycycline

Useful as an alternate to mefloquine. Side effects include GI (nausea, diarrhoea) and photosensitivity.

Dose

Adults and children >12yrs: 100mg od oral; children >8yrs: 1.5mg/kg oral od, to a max 100mg. Do not use in children <8yrs and in pregnant and lactating women.

Primaquine

Has proven in adults to be effective and safe against drug-resistant *P. falciparum* and *P. vivax*. Should be taken with food to reduce GI side effects. Should not be given to G6PD-deficient individuals or pregnant women.

Dose

0.5 base mg/kg daily for children; 30mg od as daily adult dose.

Proguanil

Used for prophylaxis in pregnant women and non-immune people in areas of low risk only. It is more commonly used in combination with chloroquine (see 'Chloroquine' later in this section). Of limited use now due to resistance.

Dose

200mg oral od in adults, including pregnant women. Children <12wks: 25mg/d; 12wks–1yr: 50mg/d; 1–4yrs: 75mg/d; 4–8yrs: 100mg/d; and 8–13yrs: 150mg/d.

A folic acid supplement should be taken during pregnancy.

Chloroquine

Used in combination with proguanil in low-risk areas, in pregnant women, and in individuals who cannot tolerate other antimalarials. Not effective against most *P. falciparum* strains worldwide; resistance in *P. vivax* is ↑.

Dose

300mg (base) oral weekly in adults, including pregnant women. Child dose chloroquine base: <12wks, 37.5mg once weekly; 12wks–1yr, 75mg weekly; 1–4yrs, 112.5mg weekly; 4–8yrs, 150mg weekly; and 8–13yrs, 225mg weekly.

Monitoring antimalarial drug resistance

With the rapid recent spread of drug resistance, there is an ↑ need to monitor the current levels of resistance to provide evidence to inform the choice of antimalarial drug therapy and ensure proper management of clinical cases. A number of monitoring systems are available.

Therapeutic efficacy testing

The WHO has developed a protocol for *in vivo* testing of the efficacy of antimalarial drugs against *P. falciparum* in the field (http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf).

In vitro resistance tests

Technologically demanding and limited by exclusion of host factors and parasite factors unrelated to resistance. These tests are useful for providing additional information to support clinical efficacy data.

Molecular markers

If the molecular basis for resistance is known, these techniques can provide early warning of the presence of resistance to a range of antimalarial tests in a parasite population and guide therapeutic choices in epidemic situations (WorldWide Antimalarial Resistance Network: http://www.wwarn.org/).

Box 2.14 Public health note: malaria control

In the late 1990s, the global malaria situation was dire—there was widespread resistance to the majority of antimalarial drugs and vector control activities were patchy and uncoordinated. From 2000 to 2015, the world saw ↑↑ antimalaria control activities including the supply and use of effective antimalarial drugs (ACTs) and of vector control (insecticide-impregnated bed nets and indoor residual spraying). This was accompanied by a ↓ in numbers of cases, with global death rates due to malaria ↓ by ~60%.

In 2015, the World Health Assembly adopted a Global Technical Strategy for malaria to provide comprehensive technical guidance to countries and development partners in achieving the goal of a world free from malaria.

The strategy is based on three pillars:

- Pillar 1. Ensure universal access to malaria prevention, diagnosis, and treatment.
- Pillar 2. Accelerate efforts towards elimination and attainment of malaria-free status.
- Pillar 3. Transform malaria surveillance into a core intervention.

Progress towards the strategies goals is tracked annually in the WHO World Malaria Report.

Potential new tools under development which could make a marked change to the global malaria situation include malaria vaccines—RTSS, the first malaria vaccine approved for use had modest efficacy in phase 3 trials and is currently undergoing large-scale pilot implementation in three countries in Africa. Other potential new tools of interest include the development of long-acting, single-dose antimalarials and the use of genetically modified mosquitos. While these approaches are exciting they are not close to application.

Full Global Technical Strategy: http://www.who.int/malaria/areas/global_technical_strategy/en/

The World Malaria Report: http://www.who.int/malaria/publications/world_malaria_report/en/

Chapter 3

HIV medicine

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Epidemiology of HIV

- The human immunodeficiency virus (HIV) is the cause of the AIDS global pandemic. AIDS was first recognized in the USA in 1981 and global mortality from HIV infection to date is >35 million.
- In 2019, 38 million people were living with HIV worldwide, including 1.8 million children. There were 1.7 million new infections, and ~0.7 million deaths. Overall, 81% of people living with HIV (PLHIV) knew their status, 67% of these were receiving antiretroviral therapy (ART), and 59% of those on ART were virologically suppressed.
- The highest HIV prevalence is in southern Africa, with rapidly increasing epidemics in Eastern Europe and in Central and East Asia.

Transmission

Potentially infectious body fluids are blood, semen, vaginal secretions, pleural and pericardial effusions, CSF, amniotic fluid, and breast milk.

Non-infectious body fluids (unless contaminated with blood) are saliva, sweat, tears, urine, vomit, and faeces.

The main routes of HIV transmission are:

- Unprotected sexual intercourse (both heterosexual and homosexual): transmission risk ↑ in the presence of sexually transmitted infections (STIs), particularly those causing genital ulceration.
- Mother-to-child transmission: the highest risk is during delivery; transmission also occurs during pregnancy and breastfeeding. In the absence of preventative treatment, the overall risk of transmission is 20–45% in breastfeeding populations.
- Infected blood products: screening of all blood products is essential.
- Sharing of needles or equipment during injecting drug use.
- Needlestick injury and other occupational exposures.

UNAIDS Global AIDS Targets

UNAIDS has developed a set of interim targets for 2025 that will enable the 2030 HIV targets within the Sustainable Development Goals to be achieved. The goals are:

- 95% of people at risk of HIV infection use appropriate person-centred, prioritised, effective combination preventative therapy by 2025
- 95% of women access sexual and reproductive health services which also ensure that pregnant and breastfeeding women have suppressed viral loads; and that 95% of HIV exposed children are tested by 2025
- 95% of people living with HIV know their status by 2025 – including all subpopulations
- 95% of people living with HIV have initiated ART
- 95% of people on ART have a suppressed viral load

In order to achieve these goals, 90% of at risk people and PLHIV need to be linked to people-centred and context-specific, integrated services; <10% of countries should have punitive legal systems that deny access to justice; <10% of PLHIV and key populations should be experiencing stigma and discrimination; and <10% of women should report inequality or violence based on their gender.

Expanding HIV testing, improving lifelong ART coverage, and affordable, accessible viral load (VL) testing with rapid regimen switch are essential to control the HIV epidemic. These can only be achieved within a wider public health response that addresses holistic healthcare needs.

Virology and immunology

HIV virology

- Enveloped RNA virus, family Retroviridae, genus *Lentivirus*.
- Spherical virions, 80–100nm in diameter, contain two identical RNA copies of genome plus three enzymes: reverse transcriptase, integrase, and protease (Fig 3.1). Two types are recognized: HIV-1 and HIV-2.
- *HIV-1* accounts for >99% of cases in the global pandemic and is divided into four groups: M, N, O, and P. Group M accounts for the majority of infections worldwide, and is itself divided into clades (e.g. clade C, predominant in southern Africa).
- *HIV-2* is a zoonotic virus of primates. It affects <0.5 million people, mainly in West Africa. HIV-2 has 40–60% genetic homology with HIV-1, is less transmissible, and causes slower CD4 and clinical decline. HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and integrase inhibitors all suppress replication, though some strains carry pre-existing PI mutations.
- Many patients with HIV-2 are co-infected with HIV-1.
- Following infection, HIV attaches to and enters immune cells that have the CD4 protein on their surface—mainly CD4 T lymphocytes and macrophages. Within these cells, the virus replicates using viral enzymes, such as reverse transcriptase and protease, as well as hijacking human cellular mechanisms for RNA and protein production. During this process, copies of viral DNA are inserted into the chromosomal DNA of the host cell. Billions of new HIV particles are formed daily in an infected person.
- The immune system responds by destroying the formed viruses, keeping circulating virus at a constant or 'setpoint'. This → a state of immune activation that persists for many years, during which the CD4 count ↓ from the normal count of 500–1400 cells/mm^3 at a rate that varies widely between individuals.
- CD4 T lymphocytes coordinate the immune response. When CD4 cell numbers are greatly depleted in the late stages of HIV infection, profound immunosuppression (AIDS) results. This → a variety of infections that would not normally cause disease in immunocompetent people—so-called opportunistic infections (OIs).
- The specific OIs that occur depend on both the geographical area and the degree of immunosuppression.
- Certain virus-associated tumours are more common in PLHIV: lymphomas (mainly due to EBV) and Kaposi sarcoma-associated herpes virus (KSHV; or human herpesvirus-8 (HHV-8)).
- AIDS-related conditions usually occur once the CD4 count is <200 cells/mm^3.
- The risk of certain infections, such as invasive pneumococcal disease and TB, are dramatically ↑ in the presence of immunosuppression due to HIV.

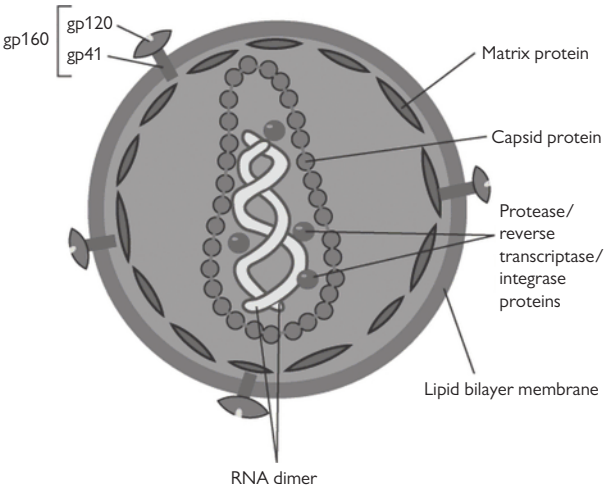

Fig. 3.1 HIV-1 virus structure. Reproduced with permission from Török, M. Estée, Cooke, Fiona J., and Moran, Ed, 'Viruses', in M. Estee Torok, Ed Moran, and Fiona Cooke, Oxford Handbook of Infectious Diseases and Microbiology (2nd edn, Oxford, 2016), Figure 8.2, © 2016, Oxford University Press.

Natural history of HIV infection

HIV infection progresses from a seroconversion illness soon after infection → a long asymptomatic period → symptomatic disease → AIDS(see Fig. 3.2).

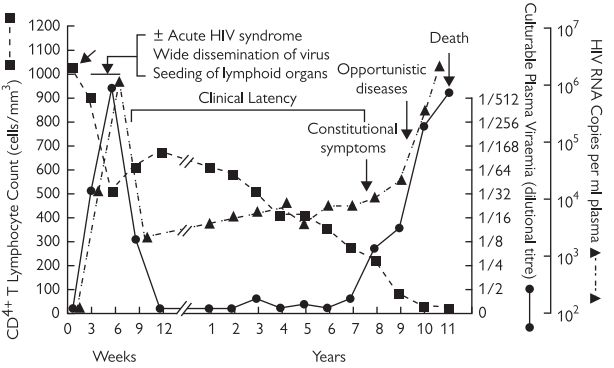

Fig. 3.2 Schematic representation of progression of HIV infection with time. Reproduced with permission from Professor Giuseppe Pantaleo, Centre Hospitalier Universitaire Vaudois.

Acute retroviral illness

- Acute retroviral illness (seroconversion illness) occurs in ~50% of patients 2–5wks after infection, and lasts 3–21d. The presentation is non-specific, and often similar to infectious mononucleosis (➲ Infectious mononucleosis, p. 737).
- Clinical features include malaise, fever, sore throat, myalgia, anorexia, arthralgia, headache, diarrhoea, nausea, lymphadenopathy, and maculopapular rash involving the trunk and arms. Atypical lymphocytes may be seen in the blood film. Rare complications include aseptic meningoencephalitis and mono/polyneuritis. HIV infection is usually not recognized at this time, and it is often misdiagnosed as another intercurrent illness (e.g. influenza).
- There may be significant temporary immunosuppression during acute infection → presentation with OIs. Serological tests for HIV are negative or indeterminate.
- There appears to be some correlation between severity of seroconversion illness and speed of HIV disease progression.

Asymptomatic HIV infection

- Seroconversion is followed by an asymptomatic stage, during which the body's immune system attempts to control the virus. HIV is not latent at this stage, but is in balance with the immune system. Billions of HIV virions are produced and destroyed each day.

Table 3.1 CD4 count and HIV complications

CD4 count	Complications
>500/mm³	Acute retroviral syndrome, *Candida* vaginitis, persistent generalized lymphadenopathy, GBS, myopathy, aseptic meningitis, TB
200–500/mm³	Pneumococcal and other bacterial pneumonia, pulmonary TB, herpes zoster, oropharyngeal candidiasis, cryptosporidiosis, Kaposi's sarcoma, oral hairy leukoplakia, cervical intraepithelial neoplasia, cervical cancer, B-cell lymphoma, anaemia, mononeuritis multiplex, idiopathic thrombocytopenic purpura, Hodgkin's lymphoma, lymphocytic interstitial pneumonitis
<200/mm³	*Pneumocystis* pneumonia (PCP), disseminated histoplasmosis or coccidioidomycosis, miliary/extrapulmonary TB, progressive multifocal leukoencephalopathy (PML), wasting syndrome, peripheral neuropathy, HIV-associated dementia, cardiomyopathy, vacuolar myopathy, progressive radiculopathy, non-Hodgkin's lymphoma (NHL)
<100/mm³	Disseminated herpes simplex, toxoplasmosis, cryptococcosis, chronic cryptosporidiosis, microsporidiosis, oesophageal candidiasis
<50/mm³	Disseminated CMV, disseminated *Mycobacterium avium* complex (MAC), primary central nervous system lymphoma (PCNSL)

- The only sign of infection during this period may be persistent generalized lymphadenopathy, but a high proportion of patients have no abnormalities on physical examination.
- The asymptomatic period varies in length, but ends when immune system dysfunction produces symptoms.

Symptomatic HIV infection

- Symptoms are often absent or non-specific until immune function becomes significantly compromised. Initial symptoms may be mild, such as skin rashes (esp. seborrhoeic dermatitis, papular pruritic eruption, or shingles) or oral candidiasis, but later the patient suffers from OIs, as well as the direct effects of HIV.
- Common symptoms include weight loss, weakness, ↓ functional capacity, diarrhoea, and peripheral neuropathy. OIs attack multiple systems. Some OIs become more common as the CD4 count falls (Table 3.1). This is reflected in the WHO staging system (Box 3.1). TB is a very common presenting illness irrespective of CD4 count; but is more severe, more likely to be disseminated, and progresses faster as CD4 count falls.
- In the absence of ART, the average time from infection to AIDS is 9yrs. Some patients are rapid progressors and may develop AIDS just a few years after infection. Typically, these patients have ↑ VL setpoints with rapid CD4 decline. Other patients may be slow progressors with slow CD4 and clinical decline.
- There is no vaccine and no cure for HIV infection. Combination ART can control viral replication, and allow a considerable and durable restoration of immune function.

WHO clinical staging of HIV disease

- This was developed for epidemiological purposes (Box 3.1). It is useful for estimating progression of HIV-related immunosuppression. Clinical stage is no longer a determinant of eligibility for ART: all PLHIV are now eligible for ART at diagnosis.
- WHO defines adults with 'advanced HIV 'as PLHIV with CD4 <200 cells/mm³ or WHO stage 3 or 4. These patients are at ↑ risk of morbidity and mortality. This can be prevented by rapid investigation, treatment, and prophylaxis of OIs and initiating ART and managing ART failure.

Box 3.1 WHO clinical staging system (2007)

Clinical stage 1
- Asymptomatic.
- Persistent generalized lymphadenopathy.

Clinical stage 2
- Weight loss <10% of body weight.
- Minor mucocutaneous lesions (seborrhoeic dermatitis, papular pruritic eruptions, fungal nail infection, recurrent oral ulceration, angular cheilitis).
- Herpes zoster.
- Recurrent URTI.

Clinical stage 3
- Weight loss >10% of body weight.
- Unexplained chronic diarrhoea for >1mth.
- Unexplained prolonged fever for >1mth.
- Oral candidiasis, chronic vaginal candida.
- Oral hairy leukoplakia.
- Pulmonary TB.
- Severe bacterial infections (pneumonia, pyomyositis, empyema).
- Acute necrotizing ulcerative oral disease.
- Unexplained anaemia (<8g/dL), neutropenia (<0.5 × 10^9/L), and/or chronic thrombocytopenia (<50 × 10^9/L).

Clinical stage 4
- HIV wasting syndrome*.
- PCP.
- Central nervous system (CNS) toxoplasmosis.
- Chronic cryptosporidiosis.
- Chronic isosporiasis.
- Cryptococcosis (extrapulmonary).
- CMV infection (retinitis or other organs).
- Chronic (>1 mth) or visceral herpes simplex virus (HSV) infection.
- PML.
- Candidiasis of the oesophagus, trachea, bronchi, or lungs.
- Disseminated non-tuberculous mycobacterial infection.
- Recurrent septicaemia including non-typhoid *Salmonella*.
- Extrapulmonary TB.
- Lymphoma (cerebral or B-cell NHL).

- Kaposi sarcoma (KS).
- HIV encephalopathy.
- Invasive cervical cancer.
- Recurrent severe bacterial pneumonia.
- Disseminated mycosis (histoplasmosis or coccidioidomycosis).
- Atypical disseminated leishmaniasis.
- Symptomatic HIV nephropathy or cardiomyopathy.

* HIV wasting syndrome: weight loss of >10%, plus either unexplained diarrhoea (lasting >1mth) or chronic weakness and unexplained fever for >1mth. Note: this is a diagnosis of exclusion: OIs must be excluded, and in patients with advanced HIV and in high-prevalence TB settings, disseminated TB is the most common cause of wasting.

HIV diagnosis

UNAIDS target is for 95% of PLHIV to know their status. Currently ~20% HIV+ve people globally remain undiagnosed so expanding testing is essential. Strategies include healthcare-based testing (in-patient settings, maternal and child health services, TB clinics, STI clinics), community-based testing (mobile and fixed site testing), and ↑ availability of self-testing with easily accessible linkage to care.

Counselling is central to HIV testing services, and must always be based on the WHO 'Five Cs':

- Consent: informed consent is essential—verbal consent is sufficient, written consent is not necessary. In patients unable to give consent due to physical or mental incapacity, many health systems allow testing without consent.
- Confidentiality.
- Counselling: pre-test group counselling can be performed, with the opportunity for further counselling in a private setting; post-test counselling must be on an individual basis.
- Correct test results: use approved algorithms for HIV testing and quality assurance.
- Connection to care: prevention, treatment, and support.

Diagnostic tests

Detection of HIV itself, or the detection of antibodies to HIV.

Direct detection of virus—nucleic acid tests (NAT; costs limit use in low- and middle-income countries)

- HIV viral DNA PCR: major use is early infant diagnosis, using dried blood spots in resource-limited settings.
- HIV viral RNA PCR.

Detection of HIV antibodies (serological tests)

- Laboratory enzyme-linked immunosorbent assay (ELISA): fourth-generation ELISA detects antibodies and p24 antigen.
- Rapid diagnostic tests: point-of-care tests, sensitivity and specificity similar to ELISA. Result available in 15–20mins. Allows same-day start of ART or linkage to care. In many settings performed by trained lay counsellors or community workers. Fourth-generation rapid tests are also available (antibodies plus p24).

Window period

- Interval between HIV infection and the test first becoming positive; this varies depending on type of test.
- Important average window periods are: HIV RNA PCR, 10d; p24 antigen ELISA/rapid test, 17d; third-generation ELISA/rapid test, 22d.
- There is wide inter-individual variation. Antibody tests are +ve in 95% of people 4–6wks after infection, and in virtually 100% by 3mths. Post-exposure prophylaxis may delay seroconversion and prolong the window period.

HIV testing strategies

To maximize the accuracy of HIV testing and prevent misdiagnosis, validated testing strategies must be used. These differ for populations with high HIV prevalence (5% or higher) or low prevalence (<5%). A single test for HIV is never sufficient to confirm HIV infection.

- High-prevalence settings: a positive result on two different tests confirms the patient is HIV+ve.
- Low-prevalence settings: a positive result on three different tests is necessary.
- The first test should have high sensitivity to avoid false negatives. The second and third tests should be different tests, and should have a high specificity to avoid false positives. Separate blood samples should be used to prevent laboratory error.
- Rapid tests can be used for all tests, but should use different antigen specificity or different platform to avoid cross-reactivity.
- WHO recommendations provide full guidance on testing strategies in high- and low-prevalence settings, including definition and management of inconclusive results.

HIV self-testing

- Enables people to collect a specimen, perform a test, and interpret the results privately. Self-testing kits of variable quality are available online and through pharmacies. Oral self-testing kits are increasingly available via national testing programmes. These use an oral swab, which is wiped over the gums.
- Has potential to reach untested, hard-to-reach, and test-averse populations; and has been shown to be widely acceptable.
- A positive result always requires further testing and confirmation by a trained tester in the context of defined national testing algorithms.
- Clear messaging is needed to inform users what to do and where to re-test if the result is positive, and that a negative test does not confirm an HIV–ve status in people at ongoing risk.

Retesting people who test HIV–ve is indicated in the following situations

- Initial HIV testing inconclusive: retest after 14d.
- PLHIV previously testing positive but not yet started on ART: to verify previous positive HIV diagnosis.
- Pregnant and breastfeeding women: seroconversion is high risk for mother-to-child transmission—in high incidence settings pregnant women testing HIV–ve should be retested in labour, and ideally every 3mths during pregnancy and breastfeeding.
- People testing HIV–ve but with ongoing risk for HIV infection: key populations, people using pre-exposure prophylaxis (PrEP).

Retesting people who are already on ART is not recommended. ART suppresses viral replication, and may also suppress the immune response to HIV and antibody production. Low antibody titres may → false-negative result.

Diagnosis of HIV-2

- Third-generation ELISAs and many rapid tests detect antibodies to HIV-1 and HIV-2 and cannot distinguish between them due to cross-reactivity. Earlier ELISAs and some rapid tests only detect HIV-1.
- In settings where HIV-2 is present, supplementary testing needs to be available.

Viral load monitoring

Quantitative HIV viral load (HIV RNA)

- Measures the amount of virus circulating in blood. Used to monitor virological suppression on ART: aim is for VL to be undetectable (often reported as LDL—lower than detectable limit, or <40 copies/mL). A high VL is defined as >1000 copies/mL.
- VL testing should be performed 3-6mths after starting first-line ART, and at least 12mthly thereafter to assess for adherence problems or resistance, and the need to switch to second line.
- HIV-1 VL assays will not detect HIV-2.

CD4 count monitoring

- Indicates the degree of immunosuppression, and the need for OI prophylaxis.
- Routine monitoring of CD4 count is no longer recommended.
- CD4 count should be requested at ART initiation, and re-checked after any period of ART interruption, if new WHO stage 3 or 4 OIs are suspected, or if there is a high VL (>1000 copies/mL).
- Point-of-care CD4 testing is increasingly available.

Antiretroviral therapy (ART): eligibility and initial investigations

All children, adolescents, and adults are eligible for lifelong ART at initial diagnosis, irrespective of CD4 count or WHO stage.

- ART blocks viral replication → ↓ virus in the blood (↓ VL) to lower than detectable levels, and allows immune restoration. CD4 count rises, and the risk of OIs is reduced.
- This 'treat all' strategy is essential to achieve UNAIDS targets of 95% of PLHIV on ART and 95% virological suppression among those on ART. Strong evidence from clinical trials has shown the benefit of starting treatment early and at high CD4 counts in terms of ↓ mortality, ↓ morbidity, and ↓ HIV transmission. ART improves both quality of life and life expectancy.

When to start

- Rapid initiation (within 7d) should be offered to all PLHIV following a confirmed HIV diagnosis and clinical assessment.
- ART initiation should be offered on the same day to people who are ready to start, and where there is no clinical contraindication (in general, treatment for OIs should begin before initiation of ART).
- Priority should be given to patients with severe or advanced disease (WHO clinical stages 3 or 4) or CD4 count ≤350 cells/mm^3, and all pregnant and breastfeeding women.

How to start

Before initiating ART

- Ensure an informed decision by the patient.
- Discuss readiness of the patient to initiate ART, the benefits and possible adverse effects of ART drugs, and adherence support.
- Discuss transmission prevention, safer sex, STIs, sexual and reproductive health (cervical cancer screening, family planning, safe conception), and disclosure.

Minimum package of investigations recommended at ART initiation

- CD4 count.
- Creatinine and calculation of creatinine clearance (CrCl): tenofovir (TDF) is contraindicated if CrCl <50mL/min.
- However, initiation of ART should not be delayed while awaiting results or if investigations are unavailable.

Additional desirable investigations include the following:

- Hepatitis B surface antigen (HBsAg); hepatitis C virus (HCV) antibodies (depending on context).
- Alanine transaminase (ALT) if nevirapine (NVP) started.
- Hb if zidovudine (AZT) initiated or if clinically anaemic.

Screening for and treating opportunistic infections

- Clinical history and examination looking for OIs, non-communicable diseases, and other illnesses (BP screening, random glucose).
- Screen for TB: fever, night sweats, weight loss, cough of any duration; or clinical features of extrapulmonary TB including neurological, respiratory, or abdominal symptoms—perform full history and examination.

- Investigate for TB if any clinical features: CXR; Xpert MTB/RIF assay (➲ Nucleic acid amplification tests, p. 153) on sputum or extrapulmonary samples; urinary lipoarabinomannan (LAM) assay if CD4 <100 or seriously ill; +/− other investigations guided by clinical picture.
- Start TB treatment if investigations confirm TB or high clinical suspicion and ongoing symptoms.
- If considered unlikely the patient has active TB, start isoniazid preventive therapy (IPT); see ➲ Prevention of opportunistic infections, p. 83.
- Treat other active OIs.

When to start ART (or switch regimens) in patients newly initiated on treatment for TB or cryptococcal disease

Tuberculosis (TB)

- Start ART within 2wks of starting TB treatment, except for TBM.
- WHO advises delaying ART by 4-8wks after starting treatment for TB meningitis (TBM) due to ↑ risk of neurological immune reconstitution inflammatory syndrome (IRIS). Corticosteroids should be considered adjuvant treatment for TBM.

Cryptococcal disease

- Cryptococcal meningitis: start ART 4–6wks after starting treatment for cryptococcal meningitis.
- Serum cryptococcal antigen test (CrAg) positive and CSF CrAg negative, or the latter not done and no neurological symptoms/signs; can start same day.

Prophylaxis

- Co-trimoxazole and IPT can be started the same day as ART.
- A fixed-dose combination (FDC) of co-trimoxazole 960mg/isoniazid 300mg/pyridoxine 25mg is increasingly available in low-resource settings.

Prevention of opportunistic infections

The optimal prevention of OIs for PLHIV is viral suppression on ART. Specific prophylaxis is described in the following subsections.

Co-trimoxazole

Prevention of PCP, toxoplasmosis, *Isospora belli* diarrhoea, and community-acquired pneumonia. Dose 960mg/d.

- Lifelong for all PLHIV in settings of high prevalence of malaria and severe bacterial infections, irrespective of WHO stage or CD4 count.
- In other settings, indicated for all with severe or advanced disease (WHO stage 3 or 4 and/or CD4 ≤350 cells/mm³). Stop when virally suppressed on ART for at least 6mths and CD4 >350 cells/mm³. Co-trimoxazole prophylaxis should be restarted if there is a new stage 3 or 4 illness or CD4 falls again to ≤350 cells/mm³.
- Co-trimoxazole is not contraindicated in pregnancy.

TB preventive treatment

- TB preventive treatment is recommended for all PLHIV without clinical evidence of active TB (negative symptom screen in ambulant patients; or negative TB investigations and clinical decision not to treat for TB if initial clinical suspicion of TB), regardless of degree of immunosuppression, ART, previous TB, or pregnancy.
- Isoniazid preventive treatment (IPT) consisting of Isoniazid (INH) 300mg od plus pyridoxine 25mg od is usually given for at least 6mths; 36mths of treatment (as a surrogate for lifelong treatment) has been shown to be beneficial in settings with high TB prevalence and risk of infection.
- An alternative is weekly rifapentine 900mg plus Isoniazid 900mg for 3 months. This is as effective as 6 mths IPT, can be used with DTG containing ART regimens, and has higher completion rates and lower risk of hepatotoxicity.
- TB preventive threrapy is of greatest benefit in people who are tuberculin skin test (TST) positive: however, this is not a requirement for initiating preventive treatment. It only prevents TB during treatment.
- IPT is *not* associated with ↑ risk of INH-resistant TB in those who go on to develop TB after stopping IPT.

Cryptococcal disease

- Screen for cryptococcal disease with serum CrAg before starting or restarting ART if CD4 <200. Give pre-emptive antifungal therapy to prevent cryptococcal meningitis if CrAg positive (➲ Cryptococcal meningitis, p. 112).
- If CrAg screening is unavailable, or if there may be prolonged delays in obtaining the result, give fluconazole 1° prophylaxis (100mg daily for 12wks) to all PLHIV with CD4 <100; consider fluconazole prophylaxis if CD4 <200.

Antiretroviral drugs

ART blocks enzymes essential for HIV replication:

- *Reverse transcriptase inhibitors*: two classes of drugs block reverse transcriptase: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The two classes have different mechanisms, therefore there is no cross-resistance between them.
- *Protease inhibitors* (PIs).
- *Integrase inhibitors* (integrase strand transfer inhibitors).

Table 3.2 lists commonly available drugs, drug abbreviations, doses, and adverse effects. Further details of important adverse effects are given in the following subsections.

General approach to managing adverse effects

Many patients starting ART experience adverse effects, esp. in the first few weeks. Most are mild and resolve spontaneously. Serious adverse effects are less common, but can rarely be life-threatening.

Before changing a single drug in a regimen, it is important to consider whether there is regimen failure (so that a regimen switch is needed) or whether a single drug substitution is possible.

- If first-line ART duration <6mths (or second-line ART <12mths), regimen failure is unlikely, and single drug substitution is fine.
- For longer treatment durations, regimen failure is possible, so VL should be checked. Often changing a drug due to adverse effects cannot wait for a VL result, so an interim decision has to be made clinically (i.e. switch regimen if clinical or immunological failure: switch one drug if the patient clinically well on ART).

Nevirapine hypersensitivity: rash and hepatitis

- Usually occurs in first 2–4wks. Risk higher if high baseline CD4 count, in women, and possibly in pregnancy. In general, avoid NVP unless there is no alternative, particularly for women with CD4 >250 cells/mL and men with CD4 >400 cells/mL.
- Rash: ranges from mild rash to severe Stevens–Johnson syndrome (toxic epidermal necrolysis).
- If mild rash with no fever, no oedema, no mucosal lesions, and no blistering of the skin, continue NVP and treat with antihistamines. Otherwise stop NVP and change to integrase inhibitor or PI. If severe rash, stop ART completely till settles; do not rechallenge with NVP and avoid EFV (same drug class, shared adverse effects though milder).
- Hepatitis: may be fulminant. Stop NVP and all other liver toxic drugs (e.g. co-trimoxazole, TB medication: rifampicin, isoniazid, pyrazinamide). Change NVP to integrase inhibitor or PI. Interrupt ART if fulminant hepatitis. Never restart NVP and avoid EFV.

Efavirenz

- Both rash and hepatitis are milder and less common with efavirenz.
- Hepatoxicity: occurs after many months; progressive, → liver failure if EFV is continued. Change to PI or dolutegravir (DTG) (check VL to see if regimen switch is needed). Never restart EFV.

- Neurological symptoms (ataxia, psychiatric symptoms) and weight loss may occur due to ↑ blood levels in people who are slow metabolizers. Symptoms resolve slowly when EFV stopped (may be 2mths) and recur if EFV restarted. Change to PI, NVP, or DTG. Never restart EFV.
- Gynaecomastia in male patients: uncommon, distressing. Change EFV to NVP, PI, or DTG (gynaecomastia may not regress, or regress only slowly; surgery required in severe cases).

Tenofovir (TDF) and renal impairment

Renal impairment occurs in <1%. Avoid if CrCl <50mL/min. However, baseline Cr and ongoing monitoring not mandatory: TDF can be used in settings without access to Cr testing.

Zidovudine (AZT) and bone marrow suppression

Usually occurs in first 3mths in patients with low CD4 counts; other causes of bone marrow suppression often coexist (TB, co-trimoxazole, malnutrition). Change to abacavir (ABC) or TDF if severe (Hb <6.5g/dL or neutrophil <500/mm³).

AZT mitochondrial toxicity (hyperlactataemia and lactic acidosis)

- Rare—was more frequent with stavudine (D4T) and didanosine (DDI) which are no longer commonly used.
- Onset after median of 9mths. Often insidious; abdominal discomfort, nausea, vomiting, ↓ weight. ↑ risk in pregnancy. Severe lactic acidosis may → Kussmaul breathing +/− circulatory collapse.
- Consider in patients who are non-specifically unwell. Check lactate and bicarbonate in symptomatic patients. If lactate >2.5mmol/L stop ART or give NNRTI plus PI until lactate normalized (2–3mths). Never restart AZT. If acidotic admit for IV fluids (also consider sepsis as cause of lactic acidosis, +/− empiric antibiotics).

Protease inhibitors: lipid and glucose abnormalities

- Some PIs (e.g. lopinavir/ritonavir (LPV/r)) → ↑ cholesterol and glucose intolerance (risk factors for cardiovascular disease) and ↑ triglycerides (risk of pancreatitis). Change LPV/r to atazanavir/ritonavir (ATZ/r) if ↑ lipids or pre-existing cardiovascular risk factors.
- Check lipids annually if possible. Treat triglycerides >10mmol/L with dietary advice + fibrate. If ↑ cholesterol and additional cardiovascular risk factors give dietary advice +/− fibrate or atorvastatin (NB some statins, e.g. simvastatin, are contraindicated with PIs as they inhibit their metabolism resulting in toxic blood levels).

Lipodystrophy: fat redistribution

- AZT may → lipoatrophy (thin limbs, loss of facial fat). PIs may → lipohypertrophy (central obesity, dorsocervical fat accumulation). Altered body shape may affect adherence; visceral fat accumulation, associated with insulin resistance and ↑ lipids.
- Management: switch to alternative agents if possible; however, reversal is slow and incomplete.

Table 3.2 ART drugs: adult doses and adverse effects

Drug	Dose	Common adverse effects
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Tenofovir (TDF)[1]	300mg od	• Renal failure: avoid if CrCl <50mL/min • Fanconi's syndrome: proximal tubular wasting of potassium, glucose, phosphate • Avoid giving with other nephrotoxic drugs for prolonged periods; e.g. aminoglycosides for TB • Active against hepatitis B
Abacavir (ABC)	600mg od or 300mg bd	• Hypersensitivity reaction: fever, rash, flu-like symptoms, GI symptoms • Low incidence of hypersensitivity in those of African origin; 5% in white population (test for HLA-B*5701 before starting—avoid ABC if HLA-B*5701 allele present) • Stop immediately if hypersensitivity suspected; never rechallenge
Zidovudine (AZT)	300mg bd	• Bone marrow suppression: anaemia, neutropenia (does not cause ↓ platelets). Usually occurs with low CD4 counts in first few months of treatment. Switch to alternative if Hb <6.5g/dL or neutrophils <0.5 × 10^9/L • Fatigue, headache, GI tract symptoms • Rare: lactic acidosis[3], myopathy, hepatic steatosis
Lamivudine (3TC)	300mg od or 150mg bd	• Well tolerated. Rarely red cell aplasia • Equivalent drug to FTC. Active against Hepatitis B
Emtricitabine (FTC)[2]	200mg od	• Well tolerated • Rarely palmar hyperpigmentation • Equivalent drug to FTC. Active against hepatitis B
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Nevirapine (NVP)	200mg bd (200mg daily 'lead-in dose' for first 2wks)	• Rash and hepatitis (ranging from mild to life-threatening[3]) • Only recommended if no alternatives • Omit 'lead-in dose' for patients already on enzyme-inducing drugs (e.g. rifampicin, switching from EFV)

Drug	Dose	Common adverse effects
Efavirenz (EFZ)	600mg od 400mg od if weight <40kg; option for all patients who are not pregnant or on TB treatment	• Rash and hepatitis (milder and less common than with NVP) • Insomnia, vivid dreams, dizziness (first 2–4wks of treatment, usually resolves). Take at night to ↓ impact of dizziness • Psychiatric symptoms—psychosis, depression. Avoid in active psychosis • Long term: hepatotoxicity, neurological problems, weight loss, gynaecomastia[3]
Protease inhibitors[4]		
Lopinavir/ ritonavir (LPV/r)	400mg/ 100mg bd Tablets are 200mg/ 50mg: 2 tablets bd	• GI symptoms very common and may impact adherence: diarrhoea, abdominal pain, nausea and vomiting • Hepatitis less common • Lipid abnormalities[3]
Atazanavir/ ritonavir (ATZ/r)	300mg/100mg od	• Fewer GI adverse effects: better tolerated than LPV/r • Unconjugated hyperbilirubinaemia: benign problem of bilirubin transport • Lipid abnormalities less common than LPV/r
Darunavir/ ritonavir (DRV/r)	600mg/100mg bd; or 800mg/ 100mg od (only if PI naïve)	• GI symptoms, rash, lipid abnormalities, hepatitis (rare) • Use with caution in sulfa allergy (contains sulphonamide moiety)
Integrase inhibitors		
Dolutegravir (DTG)	50mg od	• Insomnia, other CNS effects: less frequent than EFV • Diarrhoea, headache: usually mild, do not limit treatment • Hepatitis (particularly if HBV or HCV co-infection); hypersensitivity rare
Raltegravir (RAL)	400mg bd	• Diarrhoea, nausea, headache: usually mild, do not limit treatment • Severe adverse reactions rare: rash, hypersensitivity reactions, rhabdomyolysis

[1] NRTIs active against hepatitis B are TDF and 3TC/FTC. Dual therapy is needed to suppress replication.

[2] FTC is available as a FDC with TDF, not with ABC or AZT; single-dose tablet is of limited availability.

[3] See main text for more details.

[4] PIs are almost always co-administered with ritonavir, which inhibits metabolism of the partner PI, thereby 'boosting' its level.

ART metabolism and interactions

Renal excretion

- All NRTIs are excreted by the kidney *except* abacavir, tenofovir, lamivudine/emtricitabine, and zidovudine.
- Tenofovir causes renal impairment: avoid prescribing with other nephrotoxic drugs (e.g. aminoglycosides).
- Some drugs need dose adjustment in renal impairment (Table 3.3).

Table 3.3 ART dose adjustments in chronic renal impairment.

Antiretroviral drugs	Dose adjustment by creatinine clearance (CrCl)		
	CrCl >50	CrCl 10–50	CrCl <10
Tenofovir	300mg od	AVOID	AVOID
Abacavir	No adjustment		
Zidovudine	300mg bd	No adjustment	300mg od
Lamivudine	150mg bd or 300mg od	150mg od	50mg od
Nevirapine/efavirenz	No adjustment		
Protease inhibitors	No adjustment		
Integrase inhibitors	No adjustment		

Liver metabolism

- Efavirenz, nevirapine, and PIs are metabolized by the liver. These can cause hepatotoxicity, particularly in combination with other potentially hepatotoxic drugs (Drug-induced liver injury, p. 300).
- Drugs metabolized by the liver are an important cause of drug interactions (Table 3.4).
- Some substrates are enzyme inducers; these ↑ metabolism of other drugs, → sub-therapeutic drug levels.
- Some substrates are enzyme inhibitors, so ↓ metabolism of other drugs, → toxic drug levels.

Interactions

Important interactions between ART and commonly used drugs are shown in Table 3.5. Always check for drug interactions, particularly with PIs. See http://www.hiv-druginteractions.org for ART drug interaction information.

Table 3.4 Drugs metabolized by cytochrome P450 enzyme system

Cytochrome P450 substrates	Enzyme inducers	Enzyme inhibitors
Nevirapine/efavirenz	Nevirapine/ efavirenz	PIs
Rifampicin	Rifampicin	Macrolides
Phenytoin	Phenytoin	Cimetidine
Carbamazepine	Carbamazepine	Azoles
Phenobarbital	Phenobarbital	
Statins		
Macrolides		
Calcium channel blockers		
SSRIs (e.g. fluoxetine)		
Warfarin		
Oral contraceptives		

Table 3.5 Important interactions of ART with commonly used drugs

Drug	ART	Effect on blood level of substrate	Management
Rifampicin	Nevirapine	↓ nevirapine	Ideally use alternative drug (e.g. efavirenz). If not possible to avoid, start nevirapine at 200mg bd, rather than usual initial od 'lead-in' dose
	Lopinavir/ ritonavir	↓ lopinavir/ ritonavir	Double lopinavir/ ritonavir dose to 4 tablets bd
	Atazanavir/ ritonavir	↓ atazanavir/ ritonavir	Dose adjustment not known: do not use together Change rifampicin to rifabutin or use alternative PI
	Dolutegravir	↓ dolutegravir	Use double dose: 50mg bd
Antiepileptics: phenytoin carbamazepine phenobarbital	Efavirenz, nevirapine	↓ efavirenz ↓ nevirapine	Switch antiepileptic: use sodium valproate or lamotrigine
	AZT	↑ AZT	Watch for AZT toxicity (anaemia, neutropenia). May need to decrease AZT to 200mg bd
Amlodipine	Efavirenz, nevirapine	↓ amlodipine	Monitor BP, may need to increase amlodipine dose
	Ritonavir	↑ amlodipine	Halve the dose of amlodipine and monitor BP

Drug	ART	Effect on blood level of substrate	Management
Fluoxetine	Ritonavir	↑ fluoxetine	↓ fluoxetine dose, or use alternative (e.g. citalopram)
Simvastatin	Ritonavir	↑ simvastatin	Use alternative statin, e.g. pravastatin or atorvastatin
Oral contraceptive pill, progesterone implants	Efavirenz, nevirapine	↓ hormone levels ↑ risk of contraceptive failure	Use alternative contraception, e.g. high-dose oral contraception (oestrogen 50mcg), or long-acting injectable contraception (no interaction) or IUCD
Warfarin	Efavirenz/ nevirapine; ritonavir	↓ warfarin ↑ warfarin	Monitor INR and adjust warfarin dose accordingly

First-line ART regimens

Resistance rapidly occurs if less than three drugs are used: current regimens use three drugs for both first- and second-line therapy. Third-line regimens are individualized based on genotype, and may have more than three drugs (Second- and third-line ART, p. 96).

First-line ART: two NRTIs plus an NNRTI or integrase inhibitor

- Recommended first-line regimens are shown in Table 3.6. FDCs and once-daily regimens are preferred due to their clinical, operational, and programmatic benefits.
- *TDF + 3TC/FTC + DTG* is the preferred first-line regimen for PLHIV >6yrs old and weighing >15kg. This includes pregnant women/adolescent girls and those of childbearing age.
- DTG is available as a generic once-daily FDC together with TDF and 3TC (= TLD) in resource-limited settings.
- Clinical trials have shown that a 2NRTIs plus DTG regimen is more effective than EFV-based regimens, with more rapid viral suppression, higher CD4 recovery, and lower risk of treatment discontinuation.
- Advantages of DTG include high genetic barrier to resistance; fewer adverse effects; lower discontinuation rate, fewer drug interactions; long half-life; low cost; and activity against HIV-2 (unlike NNRTIs).
- Many PLHIV have treatment interruptions at some time due to a variety of psychosocial and economic issues. People returning to care should be 'welcomed back', with a non-judgmental approach. If ART regimen prior to interruption was while on EFV based ART, they should restart DTG based ART unless this is not available.

Table 3.6 Recommended first-line ART regimens (WHO, 2019)

Preferred regimen	Alternative regimens
▶ NRTIs + dolutegravir (DTG): TDF + 3TC (or FTC) + DTG Fixed-dose combination = 'TLD' (Note: TDF, 3TC, FTC are also active against hepatitis B)	*Substitute TDF* if renal impairment: use ABC[1] or AZT[2] *Substitute DTG* if adverse effects—options include: (a) EFV as first choice[3] (b) NVP if contraindication to EFV (e.g. psychosis)[4] (c) PI (LPV/r or ATV/r) if EFV and NVP contraindicated

[1] Avoid ABC if previous ABC hypersensitivity.

[2] Avoid AZT if anaemia (Hb <8.0).

[3] EFV_{400} contraindicated with TB treatment, pregnancy, and breastfeeding.

[4] Avoid NVP if high baseline CD4 count (↑ risk of hepatotoxicity and severe skin hypersensitivity).

Continuing ART care

What to expect in the first months of ART

- Immunological recovery and viral suppression occur in the first few months, and most patients improve clinically.
- Some patients may deteriorate due to new OIs, IRIS, or adverse drug reactions. Complications are more common in people who have advanced HIV when starting ART.
- ART significantly ↓ mortality overall, mortality remains highest in the first 3mths of ART.

Follow-up

- Monitor for adverse effects of ART, prophylaxis, and OI treatment.
- Address patients' concerns and evaluate adherence.
- Follow-up known comorbidities and OIs; ensure ongoing treatment; monitor for clinical improvement.
- Be alert for new stage 3 or 4 OIs, particularly TB; symptom screen at every clinic visit.
- Monitor VL; be vigilant for treatment failure.
- Check CD4 count if new stage 3/4 disease or VL >1000 copies/mL. Patients with advanced HIV need additional intensive follow-up in primary care, and a low threshold for hospital admission.
- WHO does not recommend any specific laboratory tests for routine monitoring of ART adverse effects. In some settings, Cr is regularly checked in patients on TDF.

Routine viral load monitoring

- Routine VL monitoring is essential to detect treatment failure early, and prevent the occurrence of new OIs and mortality.
- VL should be checked and reviewed by 6mths after starting (or re-starting) ART.
  - If VL < 50 copies/ml, repeat every 12 months
  - If VL > 50 copies/ml, repeat at 3mths after enhanced adherence counselling (see Treatment failure section and Fig 3.3 below).
- If routine VL monitoring is available, CD4 count monitoring can be stopped in people who are stable on ART and virally suppressed.
  - Point-of-care VL testing is increasingly available (Cepheid GeneXpertR Abbott m-PIMA™), enabling results and ART management on the same day as testing. However capacity is generally inadequate to provide for all VL testing; WHO therefore recommends prioritising point-of-care VL as shown in (Box 3.2):
- Virological suppression is essential for prevention of mother-to-child transmission throughout pregnancy and breastfeeding. Targeted and more frequent VL testing is essential – Box 3.3
- Targeted VL testing indicated for patients with new stage 3 or 4 OIs on ART who have not had a VL within the last 3 months.
- If VL monitoring not routinely available, CD4 count and/or clinical monitoring should be used to diagnose treatment failure, with targeted VL testing to confirm failure if possible.

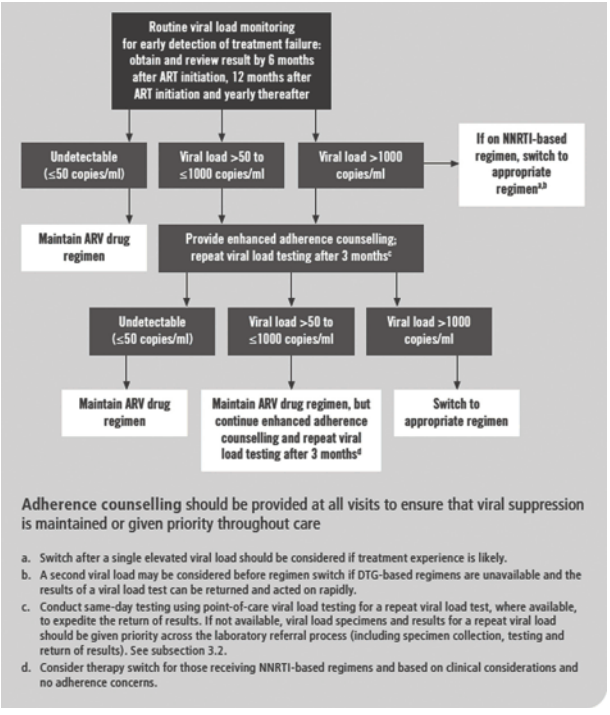

Fig. 3.3 Treatment monitoring algorithm (WHO 2021).

Box 3.2 Priorities for point of care VL testing (WHO 2021)

Point-of-care viral load testing should be prioritised for:

- Pregnant and breastfeeding women
- Infants, children and adolescents
- People requiring a repeat VL after a first elevated VL
- Suspected treatment failure
- People presenting sick, living with advanced HIV, or with a known OI (TB, cryptococcal infection, etc).

Box 3.3 Treatment monitoring in pregnancy & breastfeeding

- Whenever possible use same day point of care VL testing
- Provide adherence counselling at all antenatal and postnatal visits
- More frequent, targeted VL monitoring is indicated, including:
  - All women: at 34-36wks gestation, to identify women at risk of treatment failure and mother to child transmission.
  - If on ART before conception: at first antenatal visit if to identify women at risk of in utero transmission.
  - If starting ART during pregnancy: by 3mths after ART initiantion, to ensure rapid viral suppression.
- If VL >1000 copies/mL follow treatment monitoring algorithm (Fig. 3.3) nd provide enhanced postnatal prophylaxis for the infant. Consider infant nucleic acid testing at birth. Regardless of maternal VL, infants of mothers starting art at any time during pregnancy should be considered for testing at birth if available.
- Check VL in all breastfeeding women 3mths after delivery and every 6mths thereafter, to detect viraemia during postnatal period. If VL >1000 copies/mL, follow treatment monitoring algorithm (Fig. 3.3), test infant for HIV immediately, and consider re-initiating enhanced postnatal prophylaxis for the infant.

Treatment failure

Treatment success

The objective of ART is to block HIV replication. Treatment success is defined by VL <50 copies/mL (often reported as LDL—lower than detectable limit). This should occur within 6mths of starting ART, and continue indefinitely.

Virologic failure—when to switch to second-line ART

- Treatment failure is defined as two VLs >1000 copies/mL - the first after at least 6mths on ART, the second after 3mths, with at least 4wks of intensified adherence support following the first high VL. A repeat VL > 1,000 copies/ml requires a switch to second line ART (Fig. 3.3).
- If the patient re-suppresses after the adherence intervention, this shows that high VL was due to poor adherence alone, which had not yet caused resistance.
- VL 50-1,000 copies/ml => low level viraemia, and is a marker for predicting future treatment failure. This VL range is now included in the most recent WHO algorithm for VL monitoring (Fig. 3.3).
- There is ↑ morbidity and mortality due to delays in switching: delays often happen because it is believed there needs to be more time spent trying to optimize adherence. If poor adherence has already caused resistance, improving adherence on the current regimen will not result in viral suppression, and the clinical and immunological state of the patient will continue to deteriorate.

Role of ART regimen on decision to switch from first line ART

- Whether the ART regimen is NNRTI based or DTG based is also an important factor in the decision to switch from first line ART:
- Pre-treatment NNRTI resistance is significant in many countries, and there is evidence suggesting a large proportion (40-97%) of people taking NNRTI based regimens with a single VL > 1,000 copies/ml have drug resistance, and benefit from switching to second-line ART.
- Drug resistance is uncommon with DTG
- For people taking NNRTI based ART, a single VL > 1,000 copies/ml on NNRTI based regimen should result in a switch to DTG- based second line ART.
- Switching to DTG based second line ART should also be considered for low level viraemia (VL 50-1,000 copies/ml) on 2 consecutive VL results.
- For people taking DTG based regimens the implications of low level viraemia are unclear. There is no clear recommendation regarding switching for persistent low level viraemia. Enhanced adherence counselling should continue, and if > 2 VL results show low level viraemia, this should be discussed with a senior HIV clinician.

If VL testing not available, use the following definitions of failure

- Clinical failure: new or recurrent clinical event indicating severe immunodeficiency after 6mths of effective ART (WHO stage 4 condition, or some stage 3 conditions such as pulmonary TB or severe bacterial infections; ensure this is not IRIS).
- Immunological failure: CD4 count ≤250 following clinical failure, or persistent CD4 count <100.

Second- and third-line ART

Second-line ART

- If there is first-line failure, it should be assumed that resistance has developed to all three drugs.
- Second-line regimens also consist of three drugs:
  1. TDF or ABC in first line: change to AZT.
     AZT in first line, change to TDF or ABC.
  2. 3TC/FTC remains in second line: virus with resistance to these drugs replicates slowly, so helps to ↓VL.
  3. The third drug is from a difference class: NNRTIs are replaced with DTG or PI. DTG is replaced with PI.
- If HBsAg positive, TDF is continued as an additional drug in second line for its suppressive effect on HBV replication.

Third-line ART

- Second-line failure should only be considered after at least 1yr on PI-based second-line treatment: PIs have a high barrier to resistance, and virological failure earlier than this is very rare.
- One exception to this general rule is if there has been a drug error, including if LPV/r dose not doubled while on rifampicin-based TB treatment.
- Request genotyping if second-line failure suspected. Genotyping must be done while on the failing regimen: if ART is stopped, wild type virus replicates faster and is the predominant virus found in the blood. However mutant virus is 'archived'—mutants are never 'lost'. Once resistance to a drug has occurred, it is present lifelong, and cannot be reversed. Genotyping must be interpreted with full knowledge of all ART regimens the patient has taken.
- Third-line regimens usually include:
  - A PI (often DRV/r).
  - A drug from a class to which the patient has not previously been exposed (DTG or RAL for patients failing current first- and second-line ART).
  - Whichever NRTIs are sensitive, or to which there is low or intermediate resistance. 3TC or FTC is always included.
- Regimens must be individualized based on resistance. Genotyping is therefore essential. This is expensive, with limited availability in many resource-poor settings.
- If HBsAg positive, TDF is continued as an additional drug for its suppressive effect on HBV replication.

Advanced HIV

- Advanced HIV in adults and adolescents is defined by a WHO stage 3 or 4 event or a CD4 count <200. People with advanced HIV have ↑ risk of mortality and therefore need prioritizing for care, with rapid diagnosis and treatment if seriously ill.
- TB is the major cause of death—includes pulmonary, disseminated/miliary, and neurological TB (TB meningitis and tuberculomas).
- Other major causes of death include neurological OIs (cryptococcal meningitis, toxoplasmosis); respiratory disease (PCP, bacterial pneumonia); severe bacterial infections; and chronic parasitic diarrhoea (*Isospora belli*, *Cryptosporidium*).
- Many people with advanced HIV are ART non-naïve, and have either interrupted ART treatment for a variety of reasons, or have virological failure of first-line ART (more rarely second-line failure). This may be undiagnosed (VL not available, not done, or excessive turnaround time for results) or due to failure to switch to second-line therapy in a timely fashion.

Identifying patients with advanced HIV

- *Routine* CD4 counts are no longer recommended. However, CD4 testing is indicated for newly diagnosed PLHIV; patients initiating or reinitiating ART; VL >1000 or clinical or immunological failure; or suspicion of a new WHO stage 3 or 4 event.
- Over half of people with CD4 counts <200 are clinically well and classified as stage 1 or 2: staging alone therefore misses a substantial proportion of people with advanced HIV.

Serious illness is defined as the presence of any WHO danger signs

- Respiratory rate >30/min.
- Oxygen saturation <90%.
- Temperature >39°C.
- Heart rate >120/min.
- Inability to walk unaided.

Other signs with a high risk of mortality include:

- Systolic BP <90mmHg.
- Any new neurological presentation: confusion or other altered mental state, new focal neurology, meningism.

Package of care for advanced HIV

Screening

- Point-of-care testing: CD4 count, CrAg, TB-LAM, glucose, haemoglobin, malaria, syphilis, hepatitis B.
- Serum CrAg: if CD4 <200 (or CD4 <100 if limited availability).
- TB LAM: if CD4 <100 or signs of serious illness.

Further investigations

- Cr, electrolytes: renal failure and electrolyte abnormalities are common in advanced HIV.
- Liver function tests (LFT) if jaundice, right upper quadrant pain, or hepatomegaly.

- TB investigations: Xpert MTB/RIF (sputum and extrapulmonary samples guided by clinical picture, e.g. urine, CSF, pleural fluid).
- CSF and other body fluids (pleural effusion, ascites): cell count and differential, protein, glucose, Xpert MTB/RIF, Gram stain +/− bacterial culture; CrAg for CSF.

Treatment of OIs

- Presumptive treatment indicated if diagnostic testing not feasible, or tests cannot rule out diseases where there is a high clinical suspicion. This includes TB, toxoplasmosis, PCP, parasitic diarrhoea, and severe bacterial infections. Serum and CSF CrAg both have high sensitivity and specificity.
- For seriously ill patients, rapid recognition and treatment saves lives. A third of deaths occur within the first 48h—treat for all likely causes and ensure first doses are given without delay.
- Following hospital discharge, the mortality rate is still high, so early and frequent follow-up by HIV experienced HCW is required.

Effective ART

- Rapid initiation, re-initiation, or switch to second- (or third-) line ART is essential once OIs have been identified and treatment started.
- Current VL algorithms do not address seriously ill patients with advanced HIV: switching on the basis of clinical or immunological failure is necessary in settings where VL is not rapidly available. Waiting 3mths for a second VL is not feasible for a patient at high risk of dying.
- Enhanced adherence counselling is necessary for those returning to care or failing a regimen: adherence counselling should be done in parallel with re-initiation or switching. For people returning to care, a 'welcome back' approach is essential: being judgemental is not helpful to the patient.

Prophylaxis

Essential component of care in advanced HIV (➲ Prevention of opportunistic infections', p. 83).

Common clinical problems in HIV

Fever

- Fever is common. Causes include bacteria, mycobacteria, viruses, parasites, and fungal disease.
- TB is the most common cause. It is more likely to be disseminated at low CD4 counts and can affect any system (neurological TB, abdominal TB, and severe cachexia are common). May progress rapidly and/or present as an emergency if low CD4 count.
- Severe bacterial infections are common in seriously ill patients.
- There may be more than one cause of fever: diagnosing TB does not exclude other causes.
- Test all patients with fever for malaria in malaria endemic settings.

History

Is this a medical emergency?

- Fever + danger signs: generally acute presentation, high suspicion for bacterial infection/sepsis, malaria, and TB.

Where is the site of infection?

- Examine all systems; look for lymphadenopathy, skin disease, meningitis, respiratory, urinary tract, gynaecological, wound infection.
- There may be no localizing signs—bacteraemia and disseminated TB may present with systemic symptoms/signs (e.g. fever, wasting).

Could it be sepsis? Treat urgently with antibiotics

- Invasive bacterial infections are common in seriously ill HIV patients admitted to hospital; less common in ambulatory patients.

For seriously ill patients

- High suspicion of bacterial sepsis—low threshold for treatment.
- It can be difficult to distinguish bacterial infection from TB and other OIs: bacterial sepsis typically → fever, hypotension, tachycardia, tachypnoea, and may → altered mental state: all of these are common in disseminated TB and with other OIs.
- If available, ↑ white blood cell (WBC) count suggests bacterial infection; however, patients with advanced HIV often have bone marrow suppression due to HIV/TB, and may not show WBC response to infection, or may have infections such as non-typhi *Salmonella* that cause leucopenia.

Ambulatory patients

- There are many non-bacterial causes of fever: follow principles of antibiotic stewardship in deciding whether antibiotics are indicated.
- Common causes include:
  - *Malaria*: low threshold for testing; always take a travel history.
  - *TB*: many guidelines for TB diagnosis continue to suggest giving a course of oral antibiotics if the initial investigation for TB (sputum microscopy, Xpert MTB/RIF) are negative or not available. This delays TB treatment, and means that unnecessary courses of antibiotics. High suspicion of TB in advanced HIV should → initiation of presumptive TB treatment.

- *Persistent fever in patients taking TB treatment*: fever commonly lasts up to 14d after starting treatment. Causes of persistent fever includes poor adherence, drug reactions, drug-resistant TB, TB IRIS.
- *Other OIs*: fever is a common presenting symptom of many stage 4 OIs (cryptococcal disease, toxoplasmosis, parasitic diarrhoea, penicilliosis, visceral leishmaniasis).
- *Viral infections*: URTI and flu-like symptoms are common—and commonly → inappropriate antibiotic prescriptions.
- *Acute viral hepatitis*, or hepatitis B flare or IRIS, can → fever along with symptoms/signs of liver dysfunction.
- *Non-infectious causes*: malignancy (lymphoma, KS), venous thromboembolism (often underdiagnosed); drug hypersensitivity.
- *IRIS*: fever and tachycardia are common (➲ Immune reconstitution inflammatory syndrome, p. 121).

Investigations

- Point-of-care investigations for OIs: serum CrAg, TB LAM, VL; additional TB investigations (Xpert MTB-RIF).
- Look for organ dysfunction: anaemia, renal impairment, liver dysfunction.
- Markers of infection: WBC count; CRP is not useful for distinguishing TB and bacterial infection.
- Microbiology (if available): blood culture, microscopy/culture of urine, stool.
- If pus, lymphadenopathy, or effusions: aspirate, cell count and differential, Gram and acid-fast bacilli (AFB) stain, culture.
- LP if headache or other neurological symptoms.
- Imaging: CXR, abdominal US looking for TB (lymphadenopathy, ascites, hepatomegaly, splenic micro-abscesses, pleural effusion) or other collections.
- Biopsy of skin lesions: penicilliosis, cryptococcosis, leishmaniasis, histoplasmosis, disseminated TB.
- If fever is persistent: repeat thorough examination and available investigations; start presumptive treatment for likely causes. Giving repeated courses of antibiotics to either outpatients or inpatients with persistent fever unless there is a strong indication → antibiotic resistance and does not address the underlying cause.

Wasting

- Common; should not be ascribed to poor food intake alone.
- Cause must be identified and corrected/treated.
- Weigh patients at all visits to health services (clinic visits, hospital admissions) and record weight prominently in the notes.
- Wasting should not simply be labelled 'wasting syndrome' and no further action taken; wasting syndrome is a specific diagnosis that excludes all other causes.
- TB is the most common cause—particularly for patients who are not on effective ART.
- Other OIs are common causes—e.g. chronic parasitic diarrhoea → malabsorption.
- Give food supplements—e.g. ready-to-use therapeutic food (RUTF), soya flour, multivitamins.
- Depression is common and under-recognized in chronically ill patients with advanced HIV.

Lymphadenopathy

Differential diagnosis in advanced HIV includes:

- TB (most common cause).
- Malignancy: KS (cutaneous KS not always obvious), lymphoma.
- Fungal infection: histoplasmosis, cryptococcosis, penicilliosis.
- Visceral leishmaniasis (small volume).
- Smaller-volume lymph nodes also a more non-specific feature of HIV (persistent generalized lymphadenopathy).

Investigations

- Investigate for TB: LAM, Xpert MTB-RIF on sputum or extrapulmonary samples.
- Fine needle aspiration of lymph node: cytology for lymphoma, Xpert MTB-RIF assay for TB.
- Lymph node excision biopsy may be necessary: histology for lymphoma, KS, penicilliosis, visceral leishmaniasis.

Anaemia

- Common in advanced HIV: disseminated TB is commonest cause. Anaemia responds to treatment of TB and effective ART.
- Anaemia is not a diagnosis in itself: the underlying cause must be sought and treated.
- Most anaemia is chronic; low-resource settings often have limited availability of blood for transfusion. In most settings, transfusion is necessary only for Hb <5g/dL, or Hb <8g/dL if special circumstances (blood loss, e.g. haemoptysis, for chemotherapy or respiratory distress).

Causes—often multiple

Blood loss

- May be obvious (haemoptysis, haematemesis) or occult (e.g. in KS anaemia strongly suggests GI tract involvement, which is common).
- Women: look for gynaecological causes (cervical cancer, miscarriage, ectopic pregnancy).
- Hookworm is widely endemic, but rarely the sole cause; give empiric albendazole 400mg single dose.

Lack of production of RBC—bone marrow suppression

- Advanced HIV without effective ART.
- Disseminated TB or other OIs.
- Drugs: AZT (also causes neutropenia), co-trimoxazole (may cause pancytopenia).
- Micronutrient deficiencies: iron, folate, vitamin B_{12} (due to poor diet or malabsorption—but rarely the sole diagnosis).
- End-stage renal failure: lack of erythropoietin.

Excessive destruction of RBC

- Malaria.
- Splenomegaly from any cause.
- Drugs: rifampicin and co-trimoxazole can cause haemolysis (uncommon); resolves rapidly if drugs are stopped.

Respiratory disease

Severe respiratory disease is a common reason for hospital admission, and a common cause of mortality in advanced HIV. The three most common causes are:

- PCP.
- TB.
- Community acquired pneumonia.

All may coexist in patients with advanced HIV. There is considerable overlap in clinical presentation. If investigations such as CXR are not immediately available, treatment for all three infections should be started promptly in patients with CD4 <200 and respiratory danger signs (RR >30 breaths/min or SaO_2 <90%), together with O_2 therapy.

Pneumocystis jirovecii pneumonia

- Ubiquitous fungal infection. Usually presents with RR up to 60 breaths/min, hypoxia common. Few physical signs on respiratory examination—crepitations often absent.
- CXR: typically diffuse interstitial infiltrate without effusion or lymphadenopathy ('ground-glass' infiltrate on CT).
- Diagnosis is made on clinical and radiological grounds. Don't delay starting treatment if CXR not immediately available.
- Diagnosis may be confirmed by PCR and/or cytology on bronchoalveolar lavage (BAL) fluid, see Colour Plate 20 but rarely available or necessary in low-resource settings.

Management

- Co-trimoxazole (trimethoprim/sulfamethoxazole 80/400mg): 1 tablet for each 4kg of body weight, given in 3–4 divided doses per day.
- If RR >30 breaths/min or SaO_2 <90%, add prednisolone 40mg bd for 5d; then 40mg od for 5d; then 20mg od for 11d. Steroids prevent pulmonary fibrosis due to immunological response to dying organisms.
- After treatment, continue co-trimoxazole 960mg od 2° prophylaxis.
- *Alternative regimen* if co-trimoxazole contraindicated due to severe hypersensitivity: primaquine 15mg/d + clindamycin 600mg tds for 21d. Regimen and indications for prednisone as previously noted. Primaquine contraindicated in G6PD deficiency.
- Clinical improvement may take >1wk. Mortality is ≥20%.

Pulmonary TB

- TB is the most common cause of death in HIV. Pulmonary TB is common even at high CD4 counts; may be accompanied by extrapulmonary/disseminated TB in advanced HIV.
- Test all seriously ill patients with advanced HIV: urinary TB-LAM and Xpert MTB-RIF (sputum or non-sputum samples, e.g. urine).
- CXR: pleural effusion, pericardial effusion, lymphadenopathy. High CD4—upper zone infiltration and cavitation. Low CD4—diffuse lower zone infiltration; miliary TB.
- Start presumptive treatment if clinical suspicion high, even if tests negative or while results are awaited.
- See ➔ Chapter 4 for further details.

Community-acquired bacterial pneumonia

- Acute presentation; fever and focal signs of pneumonia.
- CXR: focal consolidation, or more diffuse 'atypical' infiltrates.
- Treat according to local antibiotic guidelines. If unavailable, give IV ceftriaxone to patients requiring hospital admission; switch to oral co-amoxiclav once improving. In severe cases, add cover for atypical pneumonia (azithromycin 500mg/d for 3d or doxycycline 100mg bd for 7d).
- See ➲ Chapter 4 for further details.

Other causes of respiratory disease in PLHIV

Frequently missed

- Pneumothorax (common complication of PCP).
- Pleural effusion.
- Pulmonary embolism.

Malignancy

- KS can present with pulmonary infiltrate or bloody pleural effusion; urgent chemotherapy is indicated.
- Lymphoma may cause mediastinal lymphadenopathy and lymphatic spread.

Pulmonary cryptococcal disease

Cryptococcus enters the body via the lungs: indistinguishable from TB on CXR. Consider in patients with pulmonary infiltrate not responding to TB treatment. Serum CrAg is positive if haematogenous spread; negative serum CrAg does not exclude diagnosis.

Lymphocytic interstitial pneumonitis

Progressive cough and dyspnoea, CXR findings indistinguishable from TB, including miliary pattern. More common in children. Responds to corticosteroids.

Other common causes

- Heart failure.
- Lung cancer or pulmonary metastases.
- Chronic lung disease (chronic obstructive pulmonary disease (COPD); pneumoconiosis in miners).
- Bronchiectasis (adolescents with congenital infection; post-TB).
- Other complications of pulmonary TB (fibrosis, aspergilloma).

Gastrointestinal disease

Diarrhoea

Common in PLHIV, particularly in advanced HIV. Chronic diarrhoea is often under-recognized, poorly managed, and resultant morbidity and mortality underappreciated (including severe dehydration → AKI, electrolyte abnormalities, malabsorption). Other symptoms may be present (e.g. nausea/vomiting, fever, abdominal pain). Diarrhoea may wax and wane, creating the illusion of response to therapy. Important causes include:

- Infections (most common; see later in this section).
- Drugs: lopinavir/ritonavir commonly → diarrhoea +/− vomiting and abdominal pain. Change to atazanavir/ritonavir or dolutegravir.

See ➲ Chapter 6 for further details on specific pathogens.

History—three key questions

1. *CD4 count*: chronic parasitic infection common if CD4 <200 (*Isospora belli*; *Cryptosporidium*; WHO stage 4 conditions); consider ART failure.
2. *Timeline*: acute (<14d) or chronic (>14d) diarrhoea?
3. *Is the diarrhoea inflammatory or non-inflammatory?*

- Inflammatory diarrhoea (large bowel):
- Abdominal cramps, fever; commonly blood + mucus in stool.
- Caused by bacteria and some parasites (e.g. amoebae).
- Non-inflammatory diarrhoea (small bowel):
  - Large volume of watery stool without blood or mucus.
  - Bacteria rarely the cause; antibiotics not indicated.

Investigations

- Cr, electrolytes.
- Hb and WBC if inflammatory diarrhoea.
- CD4 count, VL.
- Stool microscopy for ova, cysts, and parasites if available: special stains required. Some parasites (e.g. *Isospora belli*) may be shed intermittently so consider repeat testing; negative microscopy does not exclude the diagnosis. See Colour Plates 5–8.
- If diarrhoea persists despite treatment consider sigmoidoscopy, colonoscopy, or gastroscopy and biopsy.
- *Clostridium difficile* toxin if acute inflammatory diarrhoea + recent antibiotics.

General management

- Rehydration and electrolyte replacement saves lives. Low K^+ is common and may be severe. If electrolyte results not available, add 20mmol KCl to initial litre of IV fluids.
- Antibiotics if bacterial causes are strongly suspected (see later in section).
- Avoid antimotility drugs unless acute infectious diarrhoea excluded.
- Have a high suspicion of virological failure in patients with chronic diarrhoea on ART: check VL, do not delay regimen switch.

Acute diarrhoea

Non-inflammatory

- Viruses: norovirus, rotavirus.
- Bacterial: toxin secreting (cholera → large-volume rice water stools).

Inflammatory

- Fever and abdominal cramps are common; gut mucosal damage occurs in more severe disease.
- Bacteria: *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli*, *C. difficile* (recent antibiotics, hospitalized patients).
- Parasites: amoebic dysentery.

Indications for antibiotic treatment

Indications for antibiotic treatment of acute diarrhoea include:

- Fever >38°C, severe dehydration, bloody diarrhoea, visible mucus, or WBC on stool microscopy.
- Empiric regimen: ciprofloxacin for 3d; ceftriaxone is alternative.
- Treat for amoebic dysentery with 10d metronidazole if bloody diarrhoea or *Entamoeba histolytica* trophozoites seen in hot stool (Colour Plate 6a).

Chronic diarrhoea

Causes of non-inflammatory chronic diarrhoea

- *Giardia lamblia* common (➔ Giardiasis, p. 252).
- CD4 <200: *Isospora belli*, cryptosporidium, cyclospora, microsporidium; rarely these may occur at higher CD4 counts.
- *Mycobacterium avium–intracellulare* (MAC).

Treatment

- *Giardia*: tinidazole 2g PO stat; or 3d metronidazole.
- *Isospora belli*: co-trimoxazole (one 480mg tablet for each 8kg body weight per day in 2–3 divided doses) for 10d; followed by 960mg od PO 2° prophylaxis. Use ciprofloxacin 500mg bd PO if co-trimoxazole hypersensitivity. Treat pre-emptively if high clinical suspicion and/or investigations not available. Recurrent isosporiasis may occur despite immune restoration and virological suppression (possibly due to ongoing impaired gut immunity): treat with co-trimoxazole plus ciprofloxacin for 10d, then long-term maintenance co-trimoxazole 960mg bd PO.
- If persistent diarrhoea and weight loss despite co-trimoxazole and effective ART, treat presumptively for MAC with 12mths azithromycin plus ethambutol.

Causes of inflammatory chronic diarrhoea

- Parasites: amoebic dysentery; strongyloidiasis (watery, mucoid stool).
- Viral: CMV (CD4 <100). Diagnosis suggested by presence of CMV retinopathy; definitive diagnosis needs colonoscopy and biopsy.

Treatment

- Amoebiasis: metronidazole for 10d.
- Strongyloidiasis: ivermectin 200 micrograms/kg PO stat or albendazole 400mg daily for 3d.

Abdominal pain

- Abdominal TB including TB IRIS: clinical features may include ascites, lymphadenopathy, hepatomegaly, and splenic hyperdensities. Pain may be severe. Add steroids if IRIS suspected.
- Typhoid: complications, e.g. perforation more common in HIV.

- Pancreatitis (epigastric pain): causes include alcohol, drugs (antimonials, isoniazid, co-trimoxazole), CMV, TB.
- Right upper quadrant pain: liver disease (drug-induced liver injury (DILI), viral hepatitis, TB, TB IRIS), cholecystitis, HIV-related cholangiopathy.
- Gastritis and gastric ulcers are common in sick patients.
- Complications of pregnancy: ruptured ectopic pregnancy, early miscarriage.
- KS frequently involves the GI tract, → occult blood loss and anaemia +/− abdominal pain.
- Surgical causes of acute abdomen: 'pus anywhere', e.g. subphrenic abscess, liver abscess, pelvic inflammatory disease (PID; tubo-ovarian collections), psoas abscess.

Odynophagia and dysphagia

- Odynophagia suggests oesophageal candida (WHO stage 4). Give fluconazole 200mg od for 7–14d. If no response, do gastroscopy + biopsy if available; otherwise treat empirically for the following:
- Herpetic ulcers (HSV): aciclovir 400mg tds PO for 10d.
- Aphthous ulcers (common with low CD4 counts): improve with effective ART (switch regimen if ART failure suspected).
- CMV: do fundoscopy to look for CMV retinitis (usually present in patients with CMV oesophagitis). Treat with IV ganciclovir (most effective), or oral valganciclovir.

Perianal pathology

- Often very painful.
- Consider and treat *Candida* infection.
- Consider STIs and check syphilis serology; if painful ulcers treat for genital herpes (aciclovir 400mg tds PO for 7d).
- TB is a common cause of perianal fistula: biopsy and/or obtain pus for Xpert MTB/RIF and look for TB at other sites. Cultures of superficial swabs rarely helpful.
- Consider empiric antibiotics including anaerobic cover if infected-looking lesions (e.g. co-amoxiclav).
- Topical analgesia (e.g. lidocaine gel) may help but varies in efficacy.

Liver disease

Common causes of hepatomegaly

- Infections: TB, TB IRIS, visceral leishmaniasis.
- Infiltrates: lymphoma, hepatocellular carcinoma, metastases.
- Cardiac (pericardial disease; cardiac failure a common comorbidity).

HIV–hepatitis B virus co-infection

- Hepatitis B virus (HBV) is the commonest cause of acute and chronic viral hepatitis in HIV. Morbidity and mortality ↑ with HIV co-infection. Transmitted by blood and other body fluids.
- Treatment: tenofovir plus either lamivudine or emtricitabine inhibits HBV replication. Lamivudine alone or emtricitabine alone should not be used, as rapidly → resistance. Discontinuation of anti-hepatitis B drugs can → HBV flare.
- If first-line ART failure, continue tenofovir + lamivudine/emtricitabine in second-line regimen to maintain HBV suppression, and add NRTI (e.g. AZT) for HIV virological suppression.
- HBV IRIS may occur on treatment initiation, theoretically ameliorated by using NRTI with anti-HBV activity (e.g. tenofovir).

HIV–hepatitis C virus co-infection

- Hepatitis C virus (HCV) is an increasingly important cause of chronic hepatitis and cirrhosis globally, particularly in Africa and South East Asia. See ➲ Chapter 6.
- HCV infection can now be cured with short-course, oral, direct-acting antivirals. Genotype specific regimens are now available which are effective against all genotypes, and drugs are becoming cheaper. WHO recommends treatment for all adults and adolescents on diagnosis (except pregnant women).
- Treatment of HCV before commencing ART is an option in some cases if there are concerns about drug interactions or adherence.

HIV cholangiopathy

- Occurs in advanced HIV, characterized by right upper quadrant pain worse with eating, and raised alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT).
- Several potential pathogens have been implicated (*Salmonella*, CMV, *Cryptosporidium*). May → sclerosing cholangitis.
- Differential diagnosis: gallstones, abdominal TB.
- Diagnosis: clinical or imaging (endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP)).
- Treatment: effective ART; bile duct stent to relieve obstruction if severe.

Drug-induced liver injury

Common causes

- Co-trimoxazole.
- TB drugs: rifampicin, isoniazid, pyrazinamide.

- ART: NVP (more rarely efavirenz) within first 2–4wks of treatment. Efavirenz also causes a late DILI after many months of treatment, with fatal liver failure if treatment is not stopped. PIs are rarer causes, particularly ritonavir.
- May coexist with other liver disease, e.g. viral/alcoholic hepatitis.

Mild vs severe DILI

- Severe DILI—one or more of the following: bilirubin >2× normal; ALT >3× normal if symptomatic, or >5× normal if asymptomatic. Stop all hepatotoxic medication immediately. Further management depends on the clinical context (see later subsections).
- Mild DILI (not meeting any of the above-listed criteria) may be managed with treatment continuation and close monitoring of ALT, bilirubin, and symptoms.

Management of severe DILI on TB treatment

- If patient severely ill with TB, start alternative TB treatment:
  - Ethambutol *plus* levofloxacin or moxifloxacin (ciprofloxacin if no other quinolone available) *plus* kanamycin (streptomycin if no alternative; avoid aminoglycoside if renal impairment (CrCl <50)).
- Not severely ill: stop TB treatment for 1–2wks while DILI settles, then rechallenge (see next subsection).
- *Do not rechallenge if DILI has caused fulminant liver failure* (e.g. encephalopathy, coagulopathy): second- and third-line drugs usually used for drug-resistant TB will be necessary.

Rechallenging TB treatment

- Start rechallenge when bilirubin normalized and ALT <100.
- Add rifampicin to the backbone of ethambutol and a quinolone. An aminoglycoside is not necessary in the presence of three anti-TB drugs.
- Check ALT after 3d, if not ↑ add INH (start with INH if monotherapy with rifampicin is not available).
- Avoid rechallenge with pyrazinamide; prolong TB treatment to 9mths if pyrazinamide not included.

Rechallenging ART

- Stop ART until DILI settled and TB therapy successfully restarted.
- Do not rechallenge with NVP: change to a PI.
- Rechallenge with efavirenz only if mild DILI and more likely cause identified (e.g. recent TB therapy initiation); otherwise change to PI.
- Check VL to determine if regimen switch is needed.

Do NOT rechallenge co-trimoxazole

- Consider dapsone as alternative—dapsone can also cause DILI.
- Use dapsone only if mild DILI (clinically well, max. ALT <200IU/L, and bilirubin <40μmol/L). If safe to use, initiate dapsone when both TB treatment and ART have been successfully restarted.

Renal disease

Acute kidney injury

- Sepsis and dehydration are common causes. Renal function usually recovers with rehydration, but may be delayed for several weeks if acute tubular necrosis occurs—short-term dialysis may be required.
- Drugs: some drugs (e.g. rifampicin) may → interstitial nephritis. Other drug causes include co-trimoxazole, tenofovir, and amphotericin.

HIV-associated nephropathy (HIVAN)

- Results from direct infection of renal epithelial cells by HIV.
- Starts with proteinuria; may → nephrotic syndrome, ↓ renal function → end-stage renal failure over several months. Oedema and hypertensive not usually present due to tubular sodium loss.
- Diagnosis of HIVAN confirmed by histology (focal segmental glomerulosclerosis plus tubular disease). Always preferable to confirm diagnosis with renal biopsy if available as other forms of glomerulonephritis (e.g. postinfectious) may occur in PLHIV. An immune complex-mediated nephritis, distinct from focal segmental glomerulosclerosis (FSGS), has been described in association with HIV.
- Treatment: ART + angiotensin-converting enzyme (ACE) inhibitors.
- Prognosis: ART may stabilize or improve milder cases, but if renal impairment severe, the condition progresses despite ART.

Neurological disease

Neurological disease is common, has a high mortality, and is an HIV emergency. The most common and important causes include the following:

WHO stage 4 opportunistic infections

- Common: cryptococcal meningitis, toxoplasmosis, TB.
- CMV encephalitis, PML.

Other common infections

- Neurosyphilis, bacterial meningitis, cerebral malaria (➲ Cerebral malaria, p. 43).
- Bacterial sepsis is a common cause of acute confusion.

Direct effect of HIV on neurons of the central and peripheral nervous systems

- HIV encephalopathy (WHO stage 4).
- Peripheral neuropathy.

Adverse effects of HIV and TB drugs

- Efavirenz; insomnia, vivid dreams, psychosis (➲ Antiretroviral drugs: doses and adverse effects, p. 84).
- Isoniazid: neuropathy, psychosis.

Clinical presentation

Global abnormal neurology

- All the above-mentioned neurological causes may → altered mental state, ↓ consciousness, confusion, abnormal behaviour, and headache.
- Medical causes common in advanced HIV include: hypoglycaemia, hypotension, hypoxia, renal impairment, electrolyte abnormalities, liver impairment, and bacterial sepsis. There may be >1 cause.

Focal abnormal neurology

- Presentation includes hemiparesis, paraparesis, cranial nerve abnormalities, speech abnormalities, loss of vision, and ataxia.
- Common causes of space-occupying lesions are toxoplasmosis and TB (tuberculomas). These cannot be distinguished clinically.
- Less common causes include cryptococcomas, 1° CNS lymphoma, syphilitic gumma, brain abscesses.
- Inflammation of blood vessels (TB meningitis and neurosyphilis) and cranial nerves (TB meningitis) also → focal lesions.
- Other: PML, CMV.

Meningism

- Presentation includes neck stiffness, photophobia, and headache.
- Common causes: TB, cryptococcal, bacterial meningitis; signs of meningism may be absent.

Approach to diagnosis

Differential diagnosis depends on CD4 count

- TB meningitis and tuberculomas (TB space-occupying lesions) are commoner at low CD4 counts, but can occur at any CD4 count.
- CD4 <200: toxoplasmosis, cryptococcal meningitis (usually <100).
- CD4 <50: CMV, PML, 1° CNS lymphoma.

Timeline of presentation

- Acute onset (hours to days): bacterial meningitis, cerebral malaria.
- Subacute onset (days to weeks): TB, cryptococcal meningitis.

Are there symptoms/signs of disease in other systems?

- For example, is there evidence of disseminated TB?

Investigations

- Investigations often limited in low-resource settings. Given the high mortality, presumptive treatment is important.
- Point-of-care tests: glucose (check immediately if altered mental state), serum CrAg, TB LAM, malaria, syphilis, Hb.
- LP if not contraindicated (➔ Lumbar puncture and CSF interpretation, p. 113): cell count and differential, protein, glucose, CrAg, Xpert MTB-RIF, Gram stain.
- Screen all HIV+ve patients with abnormal neurology for TB.
- FBC, U&E, LFT, septic screen—e.g. urinalysis, CXR, blood culture.
- Special investigations which may be available in some settings: toxoplasmosis IgG, CMV PCR on CSF.
- Neuroimaging if available; if not readily available start presumptive treatment—this can be stopped if imaging makes a particular diagnosis unlikely (e.g. toxoplasmosis unlikely in absence of space-occupying lesion).

Presumptive management

- *Cryptococcal meningitis*: treat if CSF CrAg positive; or serum CrAg positive plus neurological symptoms/signs and LP not possible.
- *Bacterial meningitis*: treat if suggestive CSF indices (Table 3.7) and/or acute onset of meningism or acute-onset fever + neurology. Low threshold to treat if LP delayed or cannot be done.
- *Toxoplasmosis*: treat if CD4 <200 or unknown, and global or focal neurological signs.
- *TB*: high suspicion in all patients—consider presumptive treatment if no definite alternative diagnosis. TB → diverse neuropathology including meningitis with focal neurology due to vasculitis or inflammation of cranial nerves, tuberculomas, and hydrocephalus.
- *CMV encephalitis*: treat if altered mental state plus retinitis on fundoscopy; or CMV PCR positive on CSF. Use IV ganciclovir if available; oral valganciclovir is a less effective alternative.
- See ➔ p. 83 for more information on treatment of OIs.

Meningitis

See Table 3.7 for clinical and CSF findings.

TB meningitis

- Dense gelatinous exudate covers base of brain → inflammation of blood vessels and cranial nerves → focal neurology. Often insidious onset of neurological symptoms.
- CSF typically lymphocyte predominant with ↑ protein and ↓ glucose; in early TBM and TBM IRIS may be polymorph predominant. CSF Xpert MTB/RIF may be positive, but sensitivity low.
- Treatment: see ➔ TB meningitis, p. 150. High mortality and residual disability.

Cryptococcal meningitis

- Due to infection by *Cryptococcus neoformans*, a ubiquitous fungus found in soil. Infection follows inhalation of spores. Cryptococcal meningitis is a common presentation and is the leading cause of HIV-related meningitis in sub-Saharan Africa. May be prevented by fluconazole prophylaxis (➲ Prevention of opportunistic infections, p. 83).
- The thick capsule of the fungus blocks drainage of CSF via the arachnoid villi, → ↑ ICP. Disseminated cryptococcal infection can affect the skin, bone, and lungs.
- Presentation usually with insidious onset of any of: headache, malaise, fever, altered mental state. 75% of patients have ↑ ICP (>25cmH_2O). Signs of ↑ ICP may be present—these are reversible if therapeutic LP is performed urgently to remove CSF and ↓ ICP.
- Diagnosis: CrAg is highly sensitive and specific in both blood and CSF in advanced HIV (Box 3.5). India ink staining is now obsolete.
- Treatment: 2wks induction phase followed by 8wks consolidation phase, then long-term maintenance treatment.
- *Induction phase*:
  - Recommended regimen: 1wk amphotericin B 1mg/kg/d or liposomal amphotericin B 3mg/kg/d (see Box 3.4), plus flucytosine 100mg/kg/d in 4 divided doses; followed by 1wk fluconazole 1200mg/d.
  - Alternative regimens: 2wks fluconazole 1200mg/d plus flucytosine 100mg/kg/d; or 2wks amphotericin B 1mg/kg/d or liposomal amphotericin B 3mg/kg/d, plus fluconazole 1200mg/d.
- *Consolidation phase*: 8wks fluconazole 800mg od.
- *Long-term maintenance phase*: fluconazole 200mg od for at least 12mths; then continued until CD4 >100 and VL suppressed (or CD4 >200 if VL unavailable).

Therapeutic LP ↓ mortality by 69%. LP must be done in lateral position: if manometer not available attach empty open IV line to spinal needle to measure height of CSF column (CSF pressure). Opening pressure should be measured at presentation and repeated if initial pressure >30cm or ongoing/new headache, cranial nerve abnormalities, or loss of vision or hearing. Remove sufficient CSF to ↓ pressure to <20cmH_2O; remove maximum of 30mL each LP. LP may need repeating daily, or even 2× daily if severe ongoing symptoms.

Start ART 4–6wks after start of induction phase—starting earlier is associated with ↑ mortality. The same applies to switching to second-line ART in patients with first-line ART failure.

Focal neurology: space-occupying lesions

Neurological presentation depends on location of brain lesions; may be associated confusion, ↓ consciousness, or headache. In most resource-limited settings neuroimaging is limited, so base presumptive treatment on clinical suspicion.

Common causes are toxoplasmosis and TB; they cannot be distinguished clinically. Evidence of TB outside the CNS suggests TB, but does not exclude toxoplasmosis. On neuroimaging, toxoplasmosis more commonly causes multiple lesions and TB more often a single lesion; however, this is not always the case.

Table 3.7 Typical findings of common causes of meningitis in HIV

	Bacterial	TB	Cryptococcal
CD4 count	Any	Any—usually low	Usually <100
Time course	Hours to days	Days to weeks	Days to weeks
Headache	Usually	Variable	Variable
Neck stiffness	Usually	Variable	Not usually
Fever	Usually	Variable	Variable
CSF appearance	Often turbid	Clear	clear
CSF cells	Neutrophil predominance	Usually lymphocytic May be normal or mainly neutrophils in early TBM or IRIS	Variable; normal or lymphocytic
Protein	Usually high (Pandy +ve)	Usually high (Pandy +ve)	Normal or high
Glucose	Usually low	Usually low	Normal or slightly low
Special investigations	Gram stain; bacterial culture	Xpert MTB/RIF on CSF or samples (sputum, urine); mycobacterial culture	CrAg

Box 3.4 Amphotericin B

- Test doses are unnecessary; severe allergic reactions are rare.
- Renal impairment is common. Ensure adequate hydration to ↓ risk and severity—e.g. pre-hydrate with 1L normal saline + 20mmol KCl over 2h.
- Monitor K^+ as life-threatening hypokalaemia may occur; give pre-emptive K^+ supplementation.
- Use liposomal amphotericin B if available: lower incidence of side effects.
- Monitor Hb: amphotericin B inhibits erythropoietin production → anaemia.

In low-resource settings, due to the high mortality of neurological disease in advanced HIV, presumptive treatment should be given for both TB and toxoplasmosis if CD4 <200 or unknown; and for TB alone if CD4 is >200.

Less common causes include cryptococcomas, 1° CNS lymphoma, syphilitic gumma, and brain abscess.

Toxoplasmosis

Asymptomatic infection is common; many people are infected in childhood: 40–60% of adults in many countries are IgG seropositive. Latent infection → dormant cysts in the brain → reactivation in advanced HIV (CD4 <200, often <100). The lesions enlarge → neurological symptoms/signs involving any part of the brain or spinal cord. Clinical features encompass a range of global and focal neurological presentations.

Box 3.5 Serum CrAg screening

Screen prior to ART initiation or re-initiation if CD4 <200 (may use lower threshold of CD4 <100 if limited test availability). Objective is early detection and pre-emptive treatment of cryptococcal infection. If serum CrAg +ve, perform LP for CSF CrAg. Prioritize patients with symptoms/signs of meningitis. Start fluconazole 1200mg/d if LP cannot be done the same day.

- If CSF CrAg +ve, or symptoms of meningitis and LP not possible—treat for cryptococcal meningitis (➲ Cryptococcal meningitis, p. 112).
- If CSF CrAg −ve, give pre-emptive fluconazole 800mg od for 10wks (equivalent to 2wks induction phase + 8wks consolidation phase); followed by 200mg od long-term maintenance (➲ Cryptococcal meningitis, p. 112).

Diagnosis

- In the absence of neuroimaging, diagnosis is clinical—the presence of abnormal neurology in a patient with CD4 <200 or unknown.
- Toxoplasma IgG can be used to rule out toxoplasmosis—diagnosis is unlikely if toxoplasma IgG negative. Start treatment if suspected clinically—do not delay treatment while awaiting result.

Management

- Co-trimoxazole: one 80/400mg tablet for each 8kg of body weight daily, in two divided doses. Treat for 4wks, then halve this dose for 3mths; then give 480mg od maintenance therapy until CD4 >200 for at least 6mths. (Note: co-trimoxazole is non-inferior to the alternative regimen listed, is cheaper, more widely available, and has fewer side effects.)
- Alternative regimen if severe co-trimoxazole hypersensitivity: pyrimethamine 50mg od + folinic acid 10mg od + clindamycin 600mg tds for 4wks; followed by maintenance therapy with pyrimethamine 25–50mg od + folinic acid 10mg + clindamycin 300–450mg tds until CD4 >200 for at least 6mths.

Outcome

- Many patients have a rapid and full recovery, with resolution of symptoms/signs within 2–3wks. However, not all patients respond to treatment, and death or residual neurological disability may occur.

Tuberculomas

Caused by tubercles lodged in the brain that enlarge without rupturing. Treat as for TB meningitis.

Other neurological diseases in HIV

Progressive multifocal leukoencephalopathy

- White matter disease due to reactivation of latent JC virus infection. Presents with progressive and multifocal neurological symptoms: focal abnormalities, motor lesions, cranial nerve abnormalities, loss of speech, and cognitive impairment.
- Diagnosis is clinical: progressive neurological deterioration and lack of response to treatment for toxoplasmosis and TB. MRI brain and/or JC virus PCR on CSF may be requested if resources allow.
- There is no specific treatment; some patients respond to ART.

HIV-associated dementia (HIV encephalopathy)

- Slowly progressive dementia characterized by mental slowing, forgetfulness, and motor apraxias.
- Patients with acute neurological presentations may have coexisting HIV-associated dementia: however, this should not be considered the major diagnosis.
- Treatment is ART; family disclosure and support is necessary. If first-line failure proven or suspected, switch to second-line ART.

Psychosis

Psychotic symptoms are common and often multifactorial. The following are commonly implicated:

- Severe OIs, including CNS infections.
- Metabolic disorders: hyponatraemia, renal failure, liver failure.
- Medications: e.g. efavirenz, isoniazid.
- Nutritional deficiencies: vitamin B1 (thiamine), niacin or vitamin B_{12}. Treat empirically if suspected.
- Psychiatric disease should be a diagnosis of exclusion in patients with advanced HIV presenting with psychotic symptoms: investigate and treat presumptively for common OIs.

Stroke

Stroke is the abrupt onset of focal neurological deficit of vascular origin—beware of calling all hemiplegia 'stroke'. HIV-associated cerebral vasculopathy has been described, but is a diagnosis of exclusion requiring neuroimaging. Even if they have risk factors for stroke, HIV patients should be investigated for CNS OIs. Management of focal lesions should concentrate on treatable causes.

Seizures

- Even one seizure in an HIV patient needs investigation, management, and seizure control. OIs can cause seizures in addition to any other abnormal neurology. Exclude an acute metabolic cause (e.g. hypoglycaemia).
- Valproate is the recommended anticonvulsant, due to lack of interactions with ART. In an emergency, a loading dose of 10–15mg/kg can be given, oral or IV, followed by 300mg bd. Increase after 1wk to 500mg bd. Dose may be further ↑ to a maximum of 1.5g/d if breakthrough seizures occur.
- If valproate not available, give whatever anticonvulsants are available, despite drug interactions that may → inadequate levels of some NNRTIs and PIs.
- Lamotrigine is indicated for women of childbearing age if available.
- Valproate use in pregnancy is associated with developmental delay.

Peripheral neuropathy

Common at low CD4 counts: prevalence ~1/3 among patients with CD4 <200. Presentation is with ↓/altered sensation (pins and needles, burning sensation, cold legs and feet) in a 'glove and/or stocking distribution'; commonly affects the lower legs and feet. If prolonged, may → motor loss, which may be irreversible.

Common causes

- HIV neuropathy: treatment is effective ART.
- Drugs: isoniazid—due to vitamin B_6 depletion.
- CMV (often painful).
- Nutritional deficiencies: thiamine, niacin, pyridoxine, vitamin B_{12}.
- Diabetes.
- Alcohol.

Treatment

- ART (initiation, re-initiation, or switch of ART if regimen failure).
- Symptomatic pain relief; paracetamol, codeine.
- Amitriptyline: start at low dose (12.5mg nocte) and build up slowly (every 1–2wks) to max. 50mg if necessary.
- Isoniazid-induced peripheral neuropathy: pyridoxine 100mg od.
- Treat other likely vitamin deficiencies.

Acute and chronic inflammatory demyelinating polyneuropathies (incl. GBS)

- Usually occurs with high CD4 counts.
- Treat as for HIV–ve patients, and ensure effective ART.

Skin and oral disease

Itchy rashes

- Pruritic rashes are common. Consider scabies treatment even if distribution atypical, as treatment cheap and safe; see Colour Plate 19.
- Drug reactions are often itchy, but in the absence of a clear drug aetiology, consider papular dermatitis of HIV.
- Papular dermatitis of HIV: generalized itchy, fine, papular eruption ('itchy bump disease' or 'papular pruritic eruption'). May respond to topical 0.1% betamethasone valerate (1% hydrocortisone for face).

Herpes zoster

- Vesicular eruption typically in a unilateral dermatomal distribution.
- Start aciclovir (800mg 5× daily for 7d) or valaciclovir (1g 3× daily for 7d) if <72h elapsed from onset of blistering—may ↓ rash duration and ↓ risk of post-herpetic neuralgia.
- Zoster involving the eye should additionally be treated with topical aciclovir ophthalmic ointment—if possible, refer to ophthalmologist.
- Give analgesia, e.g. paracetamol +/− amitriptyline 10–25mg at night (initially 10mg nocte usually); occasionally opiates may be required.

Crusted (Norwegian) scabies

- Hyperkeratotic form of scabies seen in immunocompromise.
- Extensive crusting in areas accessible to scratching, with sparing of less accessible areas, e.g. middle of the back; scalp usually involved.
- Treatment: see ➲ Skin infestations, p. 540.

Cutaneous cryptococcosis

- Vesicular or papular rash which mimics molluscum contagiosum, although umbilication is less common.
- Diagnosis: aspiration (India ink stain or culture), skin biopsy, or serum CrAg.
- Management: as for cryptococcal meningitis (➲ Cryptococcal meningitis, p. 112).

Talaromyces marneffei (previously Penicillium marneffei)

- Common in Southeast Asia; similar skin findings to cryptococcosis.
- Initial treatment with amphotericin; itraconazole thereafter until CD4 count >100 for 6mths.

Histoplasmosis

- May present with mucocutaneous ulceration, or with a more chronic generalized crusting rash that may resemble 'chronic' impetigo.
- Diagnosis: blood culture, skin biopsy, or serum/urine antigen.
- Treatment: amphotericin or itraconazole.

Drug rashes

- Vary from mild papular eruptions to Stevens–Johnson syndrome.
- Common causes include co-trimoxazole, anti-TB drugs, and NNRTIs, but practically any drug can be involved.
- *Stop all potentially causative drugs if any danger signs present*: fever, new lymphadenopathy, facial swelling, mucosal involvement, blistering, eosinophilia, ↑ liver enzymes (any ↑ ALT with symptoms of hepatitis, or ALT >5× upper limit of normal if asymptomatic).
- Do not use drugs to treat a drug-induced skin disease—once the drug is stopped it will improve with time and supportive measures.
- Self-limiting rashes are relatively common with the NNRTIs. In patients with only mild reactions (no danger signs), consider continuing 'essential' drugs under close supervision.
- Role of steroids is uncertain in most drug rashes—but if eosinophilia present, steroids are often helpful.

Gingivostomatitis

- Common causes include *Candida* (➲ p. 600) and herpes simplex (➲ Herpes simplex, p. 565).
- Severe gingivostomatitis may occur in HIV, with extensive aphthous ulceration and necrosis. Consider topical therapy (e.g. povidone iodine mouthwashes) and oral amoxicillin plus metronidazole. In refractory cases with persistent ulceration, biopsy to exclude TB and syphilis. Persistent symptoms without an easily identifiable cause are an indication for considering ART.

Vaginal candidiasis

See ➲ *Candida* vaginitis, p. 626.

Kaposi's sarcoma

See ➲ HIV-related malignancy, p. 119.

Seborrhoeic dermatitis

See ➲ Dermatology, p. 549.

Bacillary angiomatosis

See ➲ *Bartonella*, p. 700.

HIV-related malignancy

WHO stage 4 malignancies include KS, non-Hodgkin's lymphoma (NHL), and invasive cervical cancer. There is an ↑ incidence of other malignancies in HIV, including Hodgkin's lymphoma, anal carcinoma, glioma, lung cancer, and liver cancer.

Kaposi sarcoma

- Malignancy of lymphatic endothelial cells caused by HHV8 (= KSHV).
- 1° infection is largely asymptomatic or mild flu-like illness; virus becomes latent inside cells. HIV tat protein causes replication and multicentric reactivation, resulting in multifocal KS lesions.
- May occur at any CD4 count, however generally CD4 <200.
- Wide geographical variation in HHV8 infection (~50% infection prevalence in sub-Saharan Africa).
- Incidence of KS has significantly ↓ in the ART era.

Clinical presentation

- Variable, from small numbers of skin lesions to widespread visceral involvement. Purple/brown/black skin lesions are present in 80–90% of patients with KS. These progress from macules to papules +/− ulcerating tumours. Most common sites: face, lower limbs, genitalia.
- Lymphoedema common due to lymphatic obstruction; often out of proportion to skin lesions. Swollen leg or facial oedema may be presenting complaint. Enlarged lymph nodes also common.
- Oral lesions: occur in 1/3 patients; hard palate most common site; oral lesions are a marker for visceral involvement.
- Respiratory system: dyspnoea, cough, haemoptysis, bloody pleural effusion. CXR shows flame-shaped linear and nodular infiltrates spreading from the hila.
- GI system: commonly involved: 40% at diagnosis, 80% at autopsy. Symptoms include GI tract bleeding (usually occult), abdominal pain, malabsorption; rarely intestinal obstruction. Always consider KS as a cause of anaemia in HIV.
- Other sites: liver, pancreas, bone marrow, heart (haemorrhagic pericardial effusion).
- Constitutional symptoms incl. fever, night sweats, weight loss.

Diagnosis

- Biopsy: skin lesions, lymph nodes, GI tract lesions at endoscopy.
- Clinical diagnosis if biopsy not available or treatment needed urgently: typical appearance, bloody effusion.

Treatment

- ART alone often → resolution of minor skin lesions, but complete resolution is rare in advanced disease. If ART naïve, start ART same day if possible; switch to second-line if first-line failure suspected. Avoid AZT with chemotherapy unless no alternative.
- Chemotherapy indicated for extensive skin lesions or visceral involvement. Many successful outpatient chemotherapy programmes exist in resource-limited settings. Liposomal doxorubicin or paclitaxel recommended; vincristine and bleomycin are alternatives. Urgent chemotherapy indicated if visceral involvement (e.g. pulmonary KS); often significant regression with first dose of chemotherapy. Overall survival ~50% if visceral involvement.

Non-Hodgkin's lymphoma

- CD4 usually <100 cells/mm³ (70–90% cases).
- High-grade diffuse B-cell lymphoma most common.
- HIV-related Burkitt's lymphoma occurs at wide range of CD4 counts; aggressive clinical course.

Clinical presentation

- Constitutional symptoms common (fever, sweats, weight loss).
- Lymphadenopathy often but not always present.
- Extranodal disease common: GI tract (most common), hepatic, pulmonary, bone marrow, and CNS involvement.

Diagnosis

- Biopsy of lymph node (excision biopsy), bone marrow, or other involved organs.

Treatment

- Effective ART plus chemotherapy. Median survival <1yr; 50% die from lymphoma, 50% from OIs.

Uncommon NHL variants

Prognosis poor, even with chemotherapy:

- Primary CNS lymphoma: space-occupying intracranial lesions → focal or global abnormal neurology, CD4 generally <50. Definitive diagnosis usually not possible.
- Primary effusion lymphoma (KSHV related): ascites, pleural and pericardial effusions, no solid tumour. Usually diagnosed late, if at all.

Cervical cancer

Caused by infection with human papillomavirus (HPV) serotypes 16 and 18; sexually transmitted. Progression more rapid in HIV+ve women.

Prevention is a major public health priority:

- HPV vaccine programmes are expanding. Immunization of girls aged 10–15yrs (some countries include boys).
- Cervical screening to detect pre-cancerous cervical intraepithelial neoplasia, either by visual inspection assessment of the cervix using acetic acid, or by smear cytology. Repeat cervical screening every 1–3yrs according to local guidelines.

Treatment

Precancerous lesions can be treated to prevent progression to cancer. Cervical cancer treatment includes effective ART and a combination of surgery, chemotherapy, and radiotherapy depending on stage. Prognosis is poor for advanced disease.

Immune reconstitution inflammatory syndrome

IRIS occurs due to restoration of pathogen-specific immunity following ART initiation, → an exaggerated immune response to OIs. TB is the most common OI and therefore the most common IRIS; mortality is generally low (~3%) apart from neurological TB IRIS (mortality 25–75%). Cryptococcal meningitis IRIS is next most common (mortality ~20%). Two types of IRIS are recognized:

- *Paradoxical IRIS*: OI diagnosed first and treatment started → ART initiation → clinical deterioration.
- *Unmasking IRIS*: ART initiation → clinical deterioration → new OI diagnosis.

Both types of IRIS also occur with switch to second-line ART following first-line failure.

Paradoxical TB IRIS

Occurs 48h to 3mths after starting ART; generally lasts 2–3mths, sometimes much longer. New or recurrent manifestations of TB, including:

- Fever, sweats, weight loss; tachycardia common.
- Severe acute pulmonary TB (may mimic bacterial pneumonia).
- Inflammatory lymph nodes, TB abscesses, pleural effusion.
- Abdominal pain (abdominal lymph nodes, ascites).
- Neurological problems may occur even in patients without obvious prior neurological involvement.

Risk factors

- Low CD4 count → rapid immune reconstitution with ART.
- Disseminated disease: high bacterial load → ↑ immune response.
- Short interval between initiating TB therapy and ART; however, delaying ART too long risks additional OIs, which can be fatal.

Diagnosis

- Onset within 3mths of ART.
- Diagnosis of exclusion—exclude other causes of deterioration, e.g. poor adherence, drug-resistant TB, other infections (OI, pneumonia, malaria), malignancy.

Management

- Symptomatic: analgesia; aspiration of lymph nodes/effusions.
- Only stop ART if life-threatening IRIS, e.g. neurological IRIS, ↑ respiratory distress, pericardial effusion, and tamponade.
- Steroids indicated for life-threatening IRIS, or non-life-threatening IRIS if symptoms are ongoing and interfering with daily activities (e.g. painful, large lymph nodes, abdominal pain and distention, recurrent pleural effusions). Give prednisolone 1.5mg/kg/d for 2wks, then 0.75mg/kg/d for 2wks.
- Some patients require prolonged steroids (several months)—if symptoms recur when ↓ steroid dose, ↑ dose for 2 further weeks and wean more slowly.

Unmasking TB IRIS

- Generally improves with TB therapy. Drain effusions/lymph nodes.
- Steroids rarely required—give if prolonged, severe, or neurological manifestations.

Other forms of IRIS

- *Kaposi sarcoma (KS IRIS)*—chemotherapy indicated; steroids are contraindicated as they worsen KS.
- *CMV retinitis*: give ganciclovir/valganciclovir +/− intraocular or systemic steroids.
- *Hepatitis B IRIS*: difficult to distinguish from other causes of hepatic injury (active viral hepatitis, drug injury). Steroids may be indicated in individual cases—seek advice.

HIV prevention strategies

Prevention strategies include ↓ infectious risk of PLHIV and ↓ risk of HIV–ve people acquiring HIV. Reducing high-risk behaviour is important for both approaches (safer sex campaigns, condoms, ↓ STIs, and needle exchange and opioid replacement programmes). Behavioural change is complex, and involves individuals, communities, and cultural and social factors such as sex inequality.

Prevention strategies should target key populations—these depend on local HIV epidemiology, but might include men who have sex with men (MSM), injecting drug users, people in prisons and other closed settings, sex workers, and transgender people.

Reducing infectious risk

- Virological suppression on ART prevents transmission.
- The UNAIDS slogan is 'Undetectable = Untransmittable' (U=U).

Reducing acquisition risk

- *Medical male circumcision*: ↓ infection risk by ~60% in heterosexual men: evidence for benefit is much weaker in MSM.
- *Pre-exposure prophylaxis (PrEP)*: ART *before* exposure (see next subsection).
- *Post-exposure prophylaxis (PEP)*: ART *after* exposure (see 'Post-exposure prophylaxis' later in this section).

Pre-exposure prophylaxis

- ART taken for prevention *before* a potential high-risk exposure (usually unprotected sex).
- WHO (2016) recommend oral PrEP be offered to key populations as part of combination HIV prevention approaches.
- A negative HIV test is essential before starting treatment, and should be repeated every 3mths for early detection of seroconversion.
- Start PrEP a week prior to anticipated high-risk exposure; continue for 1mth after the last high-risk encounter.
- TDF alone or TDF/3TC has been shown to be equally effective. In regions with high hepatitis B prevalence, TDF/3TC is recommended.
- Effectiveness correlates with adherence; good adherence esp. important for women. It takes 4d to achieve preventive drug levels in rectal mucosa, 7d for penile and vaginal epithelium. Vaginal levels fall rapidly after stopping PrEP.
- Development of TDF resistance as a result of PrEP has not been observed in studies to date at the time of writing.

Post-exposure prophylaxis

PEP significantly ↓ HIV transmission risk after occupational and non-occupational exposures. It should be started as early as possible—ideally within 1h; it is of no benefit if started >72h after exposure.

To pose a risk of transmission an exposure requires both potentially infectious body fluids (Table 3.8) and a high-risk mechanism/site of exposure. Table 3.9 summarizes the indications for PEP based on these factors.

Table 3.8 Infectivity of body fluids—risk of HIV transmission

Infectious—risk of transmission	Non-infectious—no risk
• Blood	• Tears
• Semen	• Sweat
• Genital secretions	• Saliva
• CSF	• Urine
• Pleural fluid	• Faeces
• Pericardial fluid	
• Amniotic fluid	
• Breast milk	

Table 3.9 Indications for PEP

Mechanism/site of exposure	HIV status of source		
	Positive	Unknown	Negative
Percutaneous exposure to blood or other infectious fluid	PEP	PEP	No PEP
Mucous membrane or open wound exposure to infectious fluid (e.g. mucosal splash injury; sexual exposure)	PEP	PEP	No PEP
Mucous membrane or open wound exposure to non-infectious fluids	No PEP	No PEP	No PEP
Intact skin exposure to *any* fluids	No PEP	No PEP	No PEP

See Table 3.8 for definitions of infectious vs non-infectious fluids.

Occupational exposure

- Almost always preventable: investigate all cases and implement risk-reduction measures to prevent similar incidents, e.g. more sharps containers, avoiding re-sheathing needles, using safety needles.
- Risk of transmission from HIV+ve source patient following hollow-bore needlestick injury is 0.3%; PEP ↓ risk by 80%.

Sexual exposure

- Unprotected sex, burst condoms, sexual assault.
- PEP is an essential component of care following sexual assault. Care should also include emergency contraception, STI treatment, and psychological interventions.

Other exposures

- Injecting drug use: sharing contaminated syringes and needles.
- Bites, punches: PEP indicated if break in the skin. For human bites, both the person bitten and the person biting are potentially exposed.
- A needle discarded some time ago ('environmental needle') has a negligible risk of transmitting HIV.

Risk of hepatitis B and C transmission

- Transmission risk higher than for HIV—after needlestick transmission risk is 6–60% for hepatitis B, and 2% for hepatitis C.
- All HCW and others at high risk (other occupational risk groups, people who inject drugs, MSM) should be fully immunized against hepatitis B.

First aid—initial management

- *Percutaneous exposure*: allow the wound to bleed freely, do not squeeze or rub injury site. Wash immediately with running water and soap or a mild non-irritant solution (avoid alcohol-based products, iodine, and bleach as these may irritate the wound).
- *Splash exposure to intact skin*: wash with running water; do not use alcohol-based antiseptics.
- *Eye splash injury*: irrigate with water or normal saline—sit in a chair, tilt head back, pour water or saline over the eye, pulling eyelids up and down to ensure all of the eye is cleaned. If wearing contact lenses, leave in place while irrigating (they help protect, by forming a barrier), then remove and clean; they are now safe to wear again.
- *Mouth splash injury*: spit fluid out immediately; rinse mouth with water or normal saline and spit out; repeat several times.

Assessment and baseline investigations

- Perform incident risk evaluation (Tables 3.8 and 3.9).
- Full documentation is important for workplace compensation (occupational exposure) and for medico-legal reasons after sexual assault.

Source baseline investigations

- HIV rapid test if status is not known: consent should be obtained.
- HBσAγ.
- Hepatitis C antibodies (high prevalence area or high-risk source, e.g. people who inject drugs).

Exposed person baseline investigations

- HIV rapid test to document baseline status.
- Hepatitis B surface antibodies (to determine immune status).
- Hepatitis C antibodies if source positive.
- Pregnancy test for women.
- Check baseline Cr if TDF is part of PEP regimen; check Hb if AZT included (use AZT only if alternatives not available).

Counselling and support

- Explain risk of HIV, risks and benefits of PEP; side effects of ART drugs; importance of adherence; anxiety management.
- Advise to use condoms until seronegative status is documented.
- For breastfeeding women, the risks and benefits need to be discussed (seroconversion has a high risk of transmission; however, HIV infection of exposed person is very unlikely if PEP is given).

PEP prescription

- Initiate PEP as early as possible following exposure (see Box 3.6 for regimens). Give first dose while awaiting source HIV test if cannot be done immediately. PEP is not needed if the source is negative, unless there is reason to suspect the source is in the window period.
- Dispense full 28d course: giving a starter pack no longer recommended due to the low rate of people returning for follow-up.
- Give HBV vaccine and HBV IgG if source HBsAg positive and exposed person HBV surface antibody negative.

Follow-up

HIV test 3mths after exposure: link to care if positive.

Box 3.6 Principles in selection of PEP regimens

- Side effect management is key to completion of PEP, and often under-managed. AZT and PIs are associated with significant side effects, and should not be used for PEP if alternatives are available. Side effects are more common in HIV–ve exposed people than in HIV+ve people initiated on ART.
- Using a three-drug regimen should not be at the expense of adherence: dual- or even single-drug regimens are still effective, and can be used if a three-drug regimen is not tolerated.

Preferred regimens

- TDF + 3TC/FTC + DTG.
- *Alternatives to DTG* if contraindicated or unavailable:
  - ATZ/r: unconjugated hyperbilirubinaemia is a common adverse effect—it is a benign condition; however, many exposed people are not willing to continue if this occurs.
  - LPV/r: use only if no alternative—GI side effects are common (diarrhoea, vomiting, abdominal pain); often poorly tolerated.
  - EFV: avoid if source is likely failing first-line ART. Insomnia, vivid dreams, and psychiatric side effects mean it is a poor choice for PEP given the high levels of anxiety.
  - *NVP must never be used for PEP* due to the ↑ risk of life-threatening side effects in people with high CD4 counts, including HIV–ve people.
- *Alternatives to tenofovir*:
  - D4T: although potentially serious, adverse effects occur late (lactic acidosis occurs at a median of 9mths); well tolerated for PEP but no longer available in many settings.
  - ABC: avoid, due to risk of hypersensitivity reactions.
  - AZT: poorly tolerated (headache, nausea); avoid if possible.

Prevention of mother-to-child transmission (PMTCT)

- In the absence of preventative measures, mother-to-child transmission of HIV occurs in 30–40% of pregnancies in a breastfeeding population. The highest risk is during delivery. Other high risk times are in the third trimester of pregnancy and during prolonged combined breast and formula feeding (mixed feeding) of the infant.

- Maternal viral suppression is the most important factor reducing mother-to-child transmission; it is also essential for maternal health. Transmission can occur even at low level viraemia.
- Advanced HIV is an under-recognized cause of maternal death in many settings, with TB being the most common underlying cause.
- Pregnancy is an immunosuppressive state and should ideally be a planned event in a woman living with HIV. It should be planned for when the mother is well, has a good CD4 count, is virologically suppressed, has good access to ART and has disclosed her status to a supportive partner.

HIV counselling and testing

- Provider-initiated counselling and testing should be available at all maternity services, from booking to the end of breastfeeding.
- All pregnant women should be offered testing at booking.
- Repeated testing of women who are initially HIV–ve is important to detect seroconversion as this presents a high risk for transmission.
- National guidelines vary, but repeated testing should be offered at least in the 3rd trimester, and/or during labour or shortly after delivery, and 3–6mthly during breastfeeding.
- Partner testing is also important: positive partners should also take ART for virological suppression to prevent seroconversion in HIV–ve women.

Management of HIV+ve pregnant and breastfeeding women

- OIs need prompt diagnosis and treatment in pregnant women. Treatment is as for non-pregnant patients.
- Women with advanced HIV should be identified and prioritized for care jointly by experienced HIV clinicians and obstetricians.

Maternal antiretroviral treatment

- ART initiation (or re-initiation following interruption): start same day if treatment ready and no suspicion of new OI. If HIV is newly diagnosed in labour, and for pregnant women not taking ART for any reason, the first dose should be given before delivery.
- ART regimens: see ➔ First-line ART regimens, p. 91, and Second- and third-line ART, p. 96.

DTG use is advised throughout pregnancy, ideally with folate supplementation to reduce the minimal risk of neural tube defects. DTG is beneficial as it is well tolerated and rapidly reduces the VL, thus reducing the risk of MTCT.

Viral load monitoring

- Routine VL monitoring is essential. For women on ART >6mths at first antenatal care visit, VL should be requested at booking if no recent result.
- Do VL at 34-36wks Gestation or at time of delivery to identify high risk babies that require enhanced PEP
- Some national guidelines recommend frequent VL monitoring during pregnancy and breastfeeding (every 3–6mths).
- If failing first- or second-line treatment, switch ART without delay.

Intrapartum care

- Caesarean section only indicated for obstetric or medical reasons.
- Universal infection control precautions should be observed during labour and delivery, as for all pregnant women.
- Avoid instrumentation (fetal scalp clips, fetal blood sampling, and instrumental delivery).

Postpartum management

- It is important that there is continuity of ART care including VL monitoring, and ongoing vigilance for OIs.
- Infants should be tested regularly. Point of care tests are preferred when available

Safe infant feeding

- National policy should promote either exclusive breastfeeding or formula feeding.
- In countries where diarrhoea, pneumonia, and malnutrition remain significant causes of child mortality, breastfeeding is recommended.
- Exclusive breastfeeding consists of breast milk alone for the first 6mths of life, followed by continued breastfeeding with appropriate complementary foods for up to 2yrs or beyond. Breastfeeding should stop only once a nutritionally adequate and safe diet without breast milk can be provided.
- There is a benefit to breastfeeding of any duration for women unable to continue for 6mths or more.

Infant ART prophylaxis

- Infant PEP during the first weeks of life prevents infection following delivery, and during breastfeeding.
- *High-risk infants* receive longer and more intensive prophylaxis, and include infants of the following mothers:
  - Received <4wks of ART at the time of delivery.
  - Mother who is poorly adherent or failing ART. This is reflected in a VL>1000copies/ml in the 4wks before delivery, or an uncorrected high VL earlier in pregnancy.
  - Women identified as HIV+ve for the first time during breastfeeding, with or without a previous negative HIV test.
- Give all high-risk infants AZT plus NVP for 6wks.
- Breastfeeding high-risk infants should continue prophylaxis for a further 6wks with either AZT plus NVP or NVP alone.
- Low-risk infants (to whom none of the above-listed high-risk criteria apply) should receive NVP alone for 6wks.

PMTCT programmes have ↓↓ transmission in some countries. However, significant challenges still remain in many settings. These include detecting seroconversion during pregnancy and breastfeeding, ensuring sustained maternal VL suppression, and facilitating safe infant feeding.

Special aspects of paediatric HIV

This section addresses some medical and psychosocial challenges of HIV in childhood (<10yrs) and adolescence (10–19yrs). It should be used alongside national guidelines both for medical protocols and to guide practice regarding the difficult issues of trust, confidentiality, disclosure, and adherence in children and adolescents**.**

Children with HIV should be managed within the context of their family structure. Parental health and active involvement in care is important for long-term treatment success of the child. Children must also be given age-appropriate information and responsibility.

More than 95% of HIV infections in children arise from mother-to-child transmission during pregnancy, delivery, and breastfeeding. PMTCT is therefore a high priority (➔ Prevention of mother-to-child transmission, p. 126).

HIV in children progresses rapidly and has a high mortality

- The immature immune system is less able to suppress viral replication, so untreated children have a higher VL than adults.
- Without ART, mortality is 30% in the 1st year of life, and 50% by 2yrs. The major causes of death are TB, PCP, gastroenteritis, and severe bacterial infections.
- Untreated HIV severely affects neurological development. HIV encephalopathy is common in children, with developmental milestones being delayed or regressing, and head circumference not increasing, or falling off the growth curve.

Early diagnosis and rapid ART initiation are therefore essential.

Advanced HIV in children—WHO definition

- All children <5yrs due to immature immune system. (CD4% is used in this age category. A CD4 <25% is considered significant)
- Adolescents and children ≥5yrs as for adults: CD4 <200 cells/mm³ or new WHO stage 3 or 4 disease (Box 3.7).

Box 3.7 WHO clinical staging for HIV in children (2010)

Clinical stage 1

- Asymptomatic.
- Persistent generalized lymphadenopathy.

Clinical stage 2

- Unexplained persistent hepatomegaly.
- Papular pruritic eruption.
- Extensive wart virus infection.
- Extensive molluscum contagiosum.
- Recurrent oral ulcerations.
- Unexplained persistent parotid enlargement.
- Lineal gingival erythema.
- Herpes zoster.
- Recurrent or URTI (otitis media, otorrhoea, sinusitis, tonsillitis).
- Fungal nail infections.

Clinical stage 3

- Unexplained moderate malnutrition not adequately responding to standard therapy.
- Unexplained persistent diarrhoea for >14d.
- Unexplained persistent fever for >1mth.
- Persistent oral candidiasis (after 6wks of life).
- Oral hairy leukoplakia.
- Acute necrotizing gingivitis/periodontitis.
- Pulmonary TB.
- Lymph node TB.
- Severe recurrent bacterial pneumonia.
- Symptomatic lymphoid interstitial pneumonitis.
- Chronic HIV-associated lung disease incl. bronchiectasis.
- Unexplained anaemia (<8g/dL), neutropenia (<0.5 × 10^9/L) and/or chronic thrombocytopenia (<50 × 10^9/L).

Clinical stage 4

- Unexplained severe malnutrition not responding to standard therapy.
- *Pneumocystis jirovecii* pneumonia (PCP).
- Recurrent severe bacterial infection (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia.
- Chronic HSV infection (orolabial or cutaneous of >1mth duration or visceral at any site).
- Extrapulmonary TB.
- KS.
- Oesophageal candidiasis (or candidiasis of the trachea, bronchi, or lungs).
- CNS toxoplasmosis (after 1mth of life).
- HIV encephalopathy.
- CMV infection, retinitis or CMV infection involving any other organ with onset after 1mth of life.
- Extrapulmonary cryptococcosis including meningitis.
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis or penicilliosis).
- Chronic cryptosporidiosis (with diarrhoea).
- Chronic isosporiasis.
- Disseminated non-tuberculous mycobacterial infection.
- Cerebral or B-cell NHL.
- PML.
- Symptomatic HIV nephropathy or cardiomyopathy.

Diagnosis of HIV in children

Early diagnosis is essential as significant mortality occurs before 3mths of age. However, clinical presentation is often non-specific (e.g. poor growth) so a high index of suspicion is essential. Mothers may seroconvert during breastfeeding and be unaware of their HIV status, so regularly test breast-feeding mothers for HIV.

Provider-initiated testing is indicated for the following children

- All children admitted to hospital in areas of high HIV prevalence.
- All HIV-exposed children (see later in section), and children of uncertain HIV exposure (orphans, abandoned children).
- Children with a parent or sibling who has HIV or has died.
- Children with clinical features of possible HIV, including persistent diarrhoea, ear discharge, oral thrush, and general lymphadenopathy.
- Children diagnosed with TB or pneumonia.
- Children with severe malnutrition.
- Children suspected to be victims of sexual assault.
- When for any other reason a clinician considers it to be in the best interests of the child.

Which tests to use in infants and children

- HIV antibodies cross the placenta, and persist until 9–18mths of age. HIV rapid tests detect antibody, and cannot distinguish maternal antibodies (HIV exposure) and infant antibodies (HIV infection).
- Nucleic acid tests (NATs) that detect viral DNA are therefore necessary to diagnose HIV infection in infants <18mths.
- Dried blood spots are frequently used to collect infant samples, which can then be sent to a centralized laboratory.
- Point-of-care testing allows same-day diagnosis and avoids delays in initiating treatment. It is strongly recommended when available, to improve mortality rates, retention in care and decrease caregiver anxiety.
- A positive NAT means the infant should immediately start ART. At the same time, NAT should be confirmed using a second sample, but ART should not be delayed while awaiting the confirmatory result.
- Management of an indeterminate NAT or discordant results (first test positive, second test negative) is a common dilemma requiring a further NAT on a third sample. Consult your lab or WHO guidelines for guidance. Always seek advice before stopping ART. ART used for PMTCT may interfere with adequate detection of HIV infection.
- Breastfed infants have an ongoing risk of HIV infection: confirmation that an infant is HIV–ve is only possible 12wks after all breastfeeding has ceased.

Testing protocol for HIV-exposed infants

- Retention in care and repeated testing and early ART initiation are essential to prevent HIV progression and mortality.
- *Birth (NAT)*: detects infants infected during pregnancy. Encouraged if possible, and allows very early initiation of ART, but may not be feasible in some low-resource settings.
- *6wks (NAT)*: detects infants infected during pregnancy or delivery (time of highest risk of HIV infection). If resources limited, give priority to testing of all infants at 6wks rather than at birth.
- *9mths (NAT)*: detects infants infected during initial months of breastfeeding. (NAT remains necessary: previous guidelines to use NAT only on infants with a positive HIV antibody test have been revised—a negative antibody test at 9mths shows maternal antibodies have been lost, but cannot rule out infant infection.)

- *>18mths and >12wks after all breastfeeding has ceased (whichever is the latest)*: HIV rapid tests can be used, and testing protocol is as for adults.

As PMTCT strategies ↓ transmission during pregnancy and delivery, around half of infant infections now occur during breastfeeding. Maternal viral suppression is the most important factor → ↓ transmission, so while testing programmes focus on the infant, VL monitoring in the mother remains a high priority to ensure success of PMTCT programmes.

Presumptive diagnosis of HIV infection

- Where NATs are not available, if an exposed child develops clinical features of HIV at <18mths or <12wks since all breastfeeding has ceased, a presumptive diagnosis of HIV should be made.
- Manage OIs and initiate ART in the usual way.
- Collect a dried blood spot for later NAT testing. If this is negative, specialist advice should be sought before stopping ART. If the child is still breastfeeding, the risk of HIV infection is ongoing.

Paediatric antiretroviral treatment

All children and adolescents are eligible for ART from the time of diagnosis, irrespective of age, CD4 count or clinical symptoms.

Management of a newly diagnosed child

Ensure HIV diagnostic protocol is followed (➲ Diagnosis of HIV in children, p. 130).

Initial assessment

- Full maternal ART and PMTCT history.
- Counselling for caregivers (and child if old enough).
- Exclude TB prior to starting ART.
- Examine for other OIs: particularly neurological and respiratory OIs.
- Measure weight, height, and head circumference.
- Neurodevelopmental assessment.
- Draw baseline bloods—CD4 and FBC.
- Start co-trimoxazole prophylaxis.
- Assess immunization status.

Subsequent consultations

- Address adherence challenges.
- Address disclosure to other family members where required.
- Address disclosure to child (step-wise age-appropriate approach; see chapter 10 in https://samumsf.org/en/resources/msf-hivtb-guide-primary-care-2018/msf-hivtb-clinical-guide-primary-care-2018).
- Continue to assess neurodevelopment/schooling challenges.
- Monitor growth and nutrition, dentition, lung health, hearing/ears, puberty and contraception requirement, and mental health.
- Assess family health—esp. parental ART adherence, and mental health.

Prescribing for children—general principles

- If history of PMTCT failure, there is a chance the infant may be infected with drug-resistant HIV. Record the antiretroviral drugs the mother has been exposed to, as well as prophylactic ART given to the infant. First-line ART regimen may need to be adjusted accordingly.

- Use an age-appropriate FDC if available. If adult FDCs must be used, take care to avoid underdosing and overdosing. Use functionally scored tablets; avoid splitting unscored tablets. Some tablets can be crushed and mixed in a little water, and some capsules can be opened—however, *not* all—read the package insert carefully.
- If possible, avoid syrups—dispersible tablets provide more accurate dosing. If syrups are used, switch to solid form as soon as possible.
- Administering medication to children can be difficult. Caregivers need counselling on how to give medication and to teach children how to swallow pills without instilling a fear of pill-swallowing.
- Some antiretroviral drugs cannot be used in young children (see Table 3.10 and following subsections).
- Dosing is weight based; doses need to be constantly adjusted as the child grows to avoid underdosing leading to drug resistance. Use national guidelines or WHO weight-based dosing charts: available at http://www.who.int/hiv/pub/guidelines/ARV2018update/en/ (annex 3).
- Keep regimen as simple as possible—use as few tablets as possible, ideally once a day.
- Adolescents face many psychosocial challenges that may impact adherence, and their needs must be understood and addressed.

First- and second-line ART regimens

See Table 3.10. Paediatric ART regimens change frequently as new formulations and weight-based dosing validations for young children become available. Check WHO and national guidelines for updates.

Diagnosis of virologic failure and switching to second-line ART

- Children may take longer than adults to virologically suppress. However suppression should be achieved by 6mths on ART.
  - Treatment failure is more common in children and adolescents (19–57% first-line ART failure by 3yrs, c.f. 10–15% in adults).
- Contributing factors incl. psychosocial challenges (stigma, lack of responsible caregiver, disclosure issues) and ART issues (e.g. complex regimens, unpleasant taste).
- Common avoidable factors incl. failure to ↑ ART doses as child grows, or to adjust for drug interactions (e.g. LPV/r and rifampicin).
- Principles of VL monitoring and diagnosing and managing virologic failure are the same as in adults (➲ Treatment failure, p. 95). Second-line ART regimens for children are given in Table 3.10.
- For children and adolescents, in addition to risk of OIs, a prolonged high VL can negatively affect neurodevelopment.

See WHO paediatric antiretroviral drug dosing chart for drug doses (➲ pp. 136–137).

Table 3.10 First- and second-line antiretroviral drug regimens

First line	Second line
Neonates (birth to 4wks)	
Preferred regimen: AZT + 3TC + RAL	Not applicable
Alternative regimens: AZT + 3TC + NVP AZT + 3TC + LPV/r (>42wks corr. gestational age)	
LPV/r poorly metabolized in premature infants and neonates up to 42wks corrected gestational age—avoid in this age group. RAL should be changed to LPV/r after a maximum of 3mths, to minimize selection for resistance to integrase inhibitors. If RAL not available, use NVP for first 4wks, then change to LPV/r.	
Children (<10yrs)	
Preferred regimen: ABC + 3TC + DTG	AZT + 3TC + ATV/r or LPV/r
Alternative regimens: ABC + 3TC + LPV/r or ATV/r	AZT +3TC + DTG
Special situations: ABC + 3TC + RAL* ABC + 3TC + EFV or NVP AZT may be used if ABC contraindicated due to hypersensitivity * RAL use may compromise later DTG use	AZT + 3TC + DTG AZT + 3TC + RAL AZT + 3TC + ATV/r or LPV/r Change AZT to TDF (children >2yrs: seek advice for <2yrs)
New formulations of ARVs are continually being produced. TAF only used for age and weight groups with approved TAF dosing DTG approved from 3kg/4weeks of age in 2020 and its use is subject to availability of the correct dispersible formulation TDF use in children is only recommended where good monitoring of bone mineral density (BMD) and Creat are available. EFV not recommended in <3yr old If using NNRTIs in infants and children with PMTCT exposure, be aware that resistance may have already developed. Monitor VL closely.	
Adolescents (10–19yrs)	
Preferred regimen: TDF + 3TC/FTC + DTG	AZT + 3TC/FTC + ATV/r or LPV/r
Alternative regimen: TDF/ABC + 3TC/FTC + EFV	2 NRTIs + DTG

Additional notes on age- and weight-related restrictions

Protease inhibitors

- LPV/r pellets should not be used in infants <6months (risk of aspiration)
- ATV/r is only approved for children ≥3mths; however, there is limited availability of formulations suitable for children <6yrs, and ritonavir needs to be given separately due to lack of an FDC. ATV/r has the advantage of being a once-daily dosage and is generally better tolerated than LPV/r.
- Darunavir is an alternative PI used in third-line, but may be used in second-line regimens for children with likely NNRTI and PI resistance, e.g. with PMTCT exposure and then failure of LPV/r or ATV/r-based regimens). Current dosage guidelines only for >3years and >10kg. Always boosted with ritonavir.
  - EFV is not recommended for children <3years and <10kg due to difficult pharmacokinetics affecting dosing.
  - Be aware of extensive resistance to NNRTIs in PMTCT exposed infants.

NRTIs

- TDF is now approved for children >2yrs, but only included in WHO preferred regimens for >30kg.
- Following TDF or ABC failure, AZT should be used to optimize NRTI backbone.

Third-line ART

- Needs specialist advice and should be based on genotyping. Third-line regimens usually include 1–2 NRTI plus darunavir/ritonavir plus DTG or RAL.

Adverse effects of ART in children

- Overall, adverse effects are similar to adults (➲ Antiretroviral drugs: doses and adverse effects, p. 135).
- NVP: hepatitis and skin hypersensitivity reactions are less common.
- EFV: CNS effects incl. vivid dreams; may → gynaecomastia with long-term use (NB physiological gynaecomastia may occur in teenage boys, which resolves spontaneously over time).
- TDF: main concerns are (1) renal impairment and (2) loss in bone mineral density. Routine monitoring is often not possible in low-resource countries; follow national guidelines.
- AZT: main adverse effect is anaemia, avoid if possible if Hb <8g/dL.
- LPV/r: both syrup and pellet formulations have bitter taste → adherence problems in children. GI side effects not common in young children, but more common in teenagers esp. in 1st 3wks. Drug interactions are common, esp. with rifampicin (Box 3.8).
- ATV can cause unconjugated hyperbilirubinaemia; this is a benign process, and not associated with liver injury. Counsel patient on the possibility of jaundice. ATV/r cannot be used with standard TB treatment.

WHO paediatric antiretroviral drug dosing chart

	AZT	3TC	ABC	NVP	EFV	RTV super-boost LPV/r		ATV + RTV	RAL	DTG	Prophylaxis
3–5.9kg	60mg bd	30mg bd	60mg bd	50mg bd	–	64mg bd (0.8mL of 80mg/mL liquid)	80/20mg bd (1mL)		25mg bd or 30mg bd (liquid) (limited data)	–5mg od (dispersible tablet)	CTX: 100/20 INH: 50mg
6–9.9kg	90mg bd	45mg bd (tablet) or 40mg bd (liquid)	90mg bd (tablet) or 80mg bd (liquid)	75mg bd (tablet) or 80mg bd (liquid)	–	96mg bd (1.2mL of 80mg/mL liquid) or 100mg bd (powder/tablet)	120/30mg bd (1.5mL)	A: 200mg od R: 80mg od (very limited data. Only use if >3mths age)	50mg bd	–10mg od	CTX: 200/40 INH: 100mg
10–13.9kg	120mg bd	60mg bd Or 120mg od	120mg bd Or 240mg od	100mg bd	200mg nocte (if older than 3years)	120mg bd (1.5mL liquid Or 100mg bd)	200/50 am 100/25 pm Or 160/40 bd	A:200mg od R:80mg od (limited data)	75mg bd Or 80mg bd (liquid)	–20mg od	CTX: 200/40 INH: 150mg
14–19.9kg	150mg bd	75mg bd Or 150mg od	150mg bd Or 300mg od	125mg bd	300mg nocte	160mg bd (liquid) Or 100mg am 200mg pm	200/50 bd	A: 200mg od R: 100 od	100mg bd	20mg od	CTX: 400/80 INH: 200mg

	AZT	3TC	ABC	NVP	EFV	RTV super-boost	LPV/r	ATV + RTV	RAL	DTG	Prophylaxis
20–24.9kg	180mg bd	90mg bd Or 180mg od	180mg bd Or 360mg od	150mg bd	300mg nocte	184mg (2.3mL liquid) bd Or 100mg am 200mg pm	200/50 bd Or 240/60 bd	A: 200mg od R: 100mg od	150 bd	50mg od	CTX: 400/80 INH: 250mg
25–34.9kg	300mg bd	150mg bd Or 300mg od	300mg bd Or 600mg od	200mg bd	400mg nocte	200mg bd	300/75mg bd	A: 300mg od R: 100mg: od	400mg bd	50mg od	CTX: 800/160 INH: 300mg
Note:				Routine use no longer recom-mended by WHO		Use if on rifampicin-containing TB Rx and LPV/r	Remember to super-boost with RTV if on TB Rx, or double dose if >10kg	Do not use with concurrent TB Rxcon taining Rifam picin		Double dose if on TB Rx	

Based on WHO 2018 guidelines. Only for children older than 4wks of age. If >35kg then full adult dosing.

DTG dosing for <20kg based on USA FDA data. Updated guidelines due later this year.

CTX, co-trimoxazole; INH, isoniazid; Rx, treatment.

TB in HIV+ve children

TB is the commonest cause of mortality in children with HIV, and all children with suspected TB must be tested for HIV. Source of TB infection is usually an adult within the household or in close regular contact with the child. HIV+ve children are more at risk of TB due to both immunosuppression and because they are more likely to be a contact of an adult with HIV/TB co-infection. See ➲ TB in children, p. 163, for general information about TB in children.

Specific features of TB in HIV+ve children

- HIV+ve children are at ↑ risk of active TB following infection; they progress more quickly from infection to disease; and are at ↑ risk of extrapulmonary TB incl. miliary TB and TBM.
- HIV+ve children should be screened for TB at every contact with healthcare, including history of TB contact, symptoms, and weight.
- Symptoms are often non-specific and most cases of pulmonary TB are smear negative, so a high index of clinical suspicion is needed.
- Bacteriological confirmation is often difficult. However, a clinical diagnosis of TB can often made on careful clinical assessment.
- *Start empiric TB treatment if there is a high clinical suspicion of TB.*

Bacteriological confirmation of TB in HIV-infected children

- *Urinary TB LAM*: indicated for all severely ill children requiring admission (irrespective of CD4 count); or CD4 <100 and symptoms or signs of TB. Xpert MTB/RIF: sputum and non-sputum samples.
- *Xpert MTB/RIF*: may be performed on induced sputum, gastric washings, LN aspirates, CSF, pleural or ascetic fluid.
- A negative TB LAM or Xpert MTB/RIF does not exclude TB.

Treatment

- TB treatment regimens are as for adults. Use weight-based dosing tables; child-friendly FDCs are available for children.
- NB ethambutol 20mg/kg/d is safe for children, regardless of age. ethionamide preferred to ethambutol in TBM for better CNS penetration.

Box 3.8 Drug interactions—rifampicin and ART

- EFV and all NRTIs: no dose adjustment needed.
- NVP: avoid with rifampicin: change NVP to PI or EFV
- LPV/r: age >5yrs, use double dose LPV/r. Age <5yrs, give additional ritonavir at 75% of the normal LPV/r dose; if single-drug ritonavir not available use triple NRTI regimen (AZT + 3TC + ABC) for duration of TB treatment (may jeopardize NRTIs for future if resistance develops).
- ATV/r: dose adjustment not determined, change to LPV/r.
- DTG: the weight-based daily dose should be give twice daily.
- RTG: child dose adjustment not determined: seek advice if no alternative.

Starting and switching ART in children with TB

- Start ART as soon as possible and within 8wks of starting TB treatment, irrespective of CD4 count or clinical stage.
- TB meningitis: delaying ART 2mths after TB therapy started associated with fewer severe adverse events compared with immediate ART.
- Regimen failure: follow above-listed recommendations for ART initiation.

Other common diseases in HIV+ve children

Have a high suspicion of TB in all severely ill HIV+ve children.

Respiratory disease

Bacterial pneumonia

- Common cause of death.
- Recurrent severe bacterial pneumonia is WHO stage 4 condition.
- TB may present as acute and/or severe pneumonia.
- Also treat for PCP if HIV-exposed/infected, esp. if age <1yr (see next subsection). Severe respiratory distress does not rule out PCP.

Pneumocystis pneumonia

- Common cause of severe, fatal pneumonia in HIV+ve children <1yr, and those that are severely immunocompromised and HIV exposed unifected children <6mths.
- Presentation: dyspnoea, ↑ RR, cyanosis +/− fever. Chest auscultation is non-specific; CXR may show diffuse infiltration or hyperinflation.
- Co-trimoxazole prophylaxis ↓ but does not completely abolish PCP risk, so cannot completely exclude diagnosis PCP.
- Treat empirically if suspected: the first dose of co-trimoxazole should be given while awaiting transfer to hospital.
- Treat with co-trimoxazole 15–20mg/kg trimethoprim plus 75–100mg/kg sulfamethoxazole IV/PO daily, in three or four divided doses for 21d. Once improving, IV may be switched to oral if no diarrhoea or malabsorption. Test and treat for concurrent CMV if resources allow.
- Give prednisolone if hypoxic or tachypnoeic: 1mg/kg bd for 5d, then 1mg/kg od for 5d, then 0.5mg/kg od for 5d.
- Give co-trimoxazole prophylaxis once treatment complete.

Lymphocytic interstitial pneumonitis

- Rare <1yr, usually presents in 2nd or 3rd year of life in child not on ART.
- Presentation: cough, dyspnoea, fever (differential diagnosis TB); symmetrical lymphadenopathy, clubbing, parotid enlargement.
- CXR features include reticulonodular shadowing, and bilateral hilar lymphadenopathy (without airway compression).
- Treatment is with corticosteroids.

Neurological disease

TB meningitis

- High mortality; significant morbidity. Start early empiric treatment if suspected. Prefer ethionamide to ethambutol.

Bacterial meningitis

- Common in HIV; symptoms may be non-specific, e.g. fever, vomiting.
- Start empiric antibiotics promptly if suspected.

Cryptococcal meningitis

- Rare in children. Usually in older HIV+ children not on ART. Routine screening and 1° prophylaxis are not recommended. Diagnosis is as for adults (➲ Cryptococcal meningitis, p. 112).
- Measurement of CSF opening pressure and therapeutic LP are essential, and reduce mortality.
- Treatment—see Box 3.9.
- As for adults, ART initiation (or regimen switch) should be delayed 4–6wks from initiation of antifungal treatment.

HIV encephalopathy

- Caused by HIV infection of neural cells. May be the first indication a child is HIV+ve. Recognition important as early diagnosis and ART can ↓ long-term sequelae.
- Suspect if head circumference not increasing as expected; and/or if developmental milestones are delayed or have regressed.
- Diagnosis of exclusion: investigate for TB and other OIs. Important differential diagnoses include TB arachnoiditis or spinal TB. HIV encephalopathy is not a cause of acute neurological deterioration.
- Multidisciplinary approach important: initiate ART (switch regimen if ART failure), psychosocial support, and physiotherapy.
- May → HIV myelopathy with spastic diplegia.

Box 3.9 Treatment of cryptococcal meningitis in children

Induction regimen

- Preferred regimen: amphotericin B (1mg/kg/d) plus flucytosine (100mg/kg/d, in 4 divided doses) for 1wk; followed by fluconazole 12mg/kg/d (max. 800mg daily) for 1wk.
- Alternative regimens, depending on drug availability:
  - Flucytosine (100mg/kg/d, in four divided doses) plus fluconazole (12mg/kg/d, max. 800mg daily) for 2wks; or
  - Amphotericin B (1mg/kg/d) plus fluconazole (12mg/kg/d, max. 800mg daily) for 2wks.

Consolidation phase

- Fluconazole 6–12mg/kg/d (max. 800mg daily) for 8wks.

Maintenance

- Fluconazole 6mg/kg/d.

Criteria for discontinuation of maintenance therapy

- Children >5yrs (VL monitoring available): stable on and adherent to ART and fluconazole for at ≥1yr, CD4 ≥100, and fully suppressed VL.
- Children >5yrs (VL monitoring not available): stable on and adherent to ART and fluconazole for ≥1yr and CD4 ≥200.
- Children 2–5yrs: stable on and adherent to ART and fluconazole for ≥1yr, and CD4 percentage >25% or absolute CD4 ≥750.
- Children <2yrs: maintenance treatment should not be discontinued.

Prevention of opportunistic infections in children

Co-trimoxazole

For prevention of PCP, bacterial pneumonia, toxoplasmosis, diarrhoea, and malaria. See Box 3.10.

Box 3.10 Co-trimoxazole prophylaxis dosing in children

There are two widely available formulations:

- Suspension of 40mg trimethoprim/200mg sulfamethoxazole per 5mL.
- Tablets of 80mg trimethoprim/400mg sulfamethoxazole.
- Dosing is weight-based:
  - 3.0–4.9kg: 2.5mL daily.
  - 5.0–13.9kg: 5mL daily.
  - 14.0–29.9kg: 10mL daily, or 1 tablet daily.
  - >30kg: 2 tablets daily.

Indications

- Give to all HIV-exposed infants from 6wks of age.
- Can be stopped after a definitive HIV-negative test (taken at least 12wks after all breastfeeding has stopped and >6mths of age).
- For HIV+ve infants, continue for life (countries where bacterial infections and malaria are common); if country guidelines do not recommend life-long prophylaxis, stop in children >5yrs after a minimum of 12mths ART, with two consecutive CD4 counts >200.

Isoniazid preventative therapy (IPT)

- Give IPT to all HIV exposed children <5yrs, and all HIV+ children (irrespective of age) with household contact with drug-sensitive TB.
- Exclude active TB before initiating (in practice, this means a well child without clinical suspicion of TB).
- Dose: isoniazid (10mg/kg daily, max. 300mg/d) plus pyridoxine (<5yrs 12.5mg daily; >5yrs, 25mg daily), both for 6mths.
- Repeat IPT if there is a further exposure (also indicated even if immediately after TB treatment has been completed).
- In neonates whose mother has active TB, start empiric TB treatment rather than IPT if there is any clinical suspicion of TB.

Additional prophylaxis

Follow national guidelines: may include multivitamins, repeated doses of vitamin A,immunisations and regular deworming with albendazole/mebendazole.

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Tuberculosis

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Tuberculosis trends, challenges, and lessons

TB has been curable for >50yrs, yet 10 million people develop active TB and 1.7 million people die of TB globally each year—most in LMICs. TB is strongly linked to poverty and 75% of patients are aged 15–50yrs, with a high incidence in exposed infants. Treatment is highly effective in curing disease and preventing transmission.

Important challenges and developments include the following:

- Despite widespread ART that ↓ TB risk, TB incidence remains high in high HIV prevalence areas. HIV prevention and ↑ ART are important to further ↓ TB incidence.
- ↑ drug resistance (driven by economic and political instability and weak TB programmes) has ↓ cure rates, making TB control more difficult and expensive.
- New TB diagnostics and medications provide opportunities to improve detection and control.
- TB is a major contributor to under-five mortality, but is often classified as 'pneumonia', 'meningitis', or 'malnutrition' deaths.

In 2015, the WHO launched their End TB Strategy (Box 4.1). See also Box 4.2.

Box 4.1 Elements of the WHO End TB Strategy (2016–2035)

- *Pillar 1. Integrated patient-centred care and prevention:*
  - Early TB diagnosis incl. universal drug susceptibility testing; systematic screening of multidrug resistant (MDR) contacts and high-risk groups.
  - Universal treatment incl. for drug-resistant TB; patient support.
  - Collaborative TB/HIV activities; management of comorbidities.
  - Preventive treatment of high-risk groups; TB vaccination.
- *Pillar 2. Bold policies and preventive treatment:*
  - Political commitment and adequate resources for treatment and prevention.
  - Widespread stakeholder engagement.
  - Universal healthcare policy with regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control.
  - Social protection, poverty alleviation, and action against other determinants of TB.
- *Pillar 3. Intensified research and development, including:*
  - Discovery, development, and rapid uptake of new tools, interventions, and strategies.
  - Research to optimize implementation and impact; and promote innovations.

Box 4.2 Lessons learned in TB treatment and control

TB-related deaths fell 100-fold in Europe and the USA between 1900 and 1980. Between 1995 and 2010 ~46 million patients were successfully treated through directly observed therapy, short-course (DOTS) programmes, which ↑ treatment success rate from 57% to 87% among smear +ve cases. Several lessons can be drawn from these experiences:

- The public sector has responsibility for ensuring TB treatment and control, usually through a national TB programme.
- TB treatment should be provided free of charge. Where possible, patients should be spared all costs of TB diagnosis and treatment.
- TB treatment and control must be integrated within the general health services, since that is where TB cases present.
- Collaboration between TB and HIV programmes is essential.
- For good TB control, the social determinants of TB must be tackled, incl. poverty, housing, and costs of diagnosis/treatment.
- Infants should be immunized with BCG (➲ BCG, p. 147).
- Secure an uninterrupted supply of essential TB drugs.
- Establish a reliable monitoring, recording, and reporting system.

TB control programmes

TB control programmes require a structure, usually at national level, to coordinate regimens, protocols, training, drug supply, laboratory quality assurance, and monitoring of outcomes.

Detecting and curing smear +ve PTB cases, which are the most infectious, is an effective means to ↓ TB transmission. Accordingly, a key priority of a TB programme is to achieve a high rate of treatment success among smear +ve PTB cases. Poor treatment → ↑ transmission and ↑ drug resistance. Once a TB programme is achieving >85% treatment success, the next priority is to ↑ case finding.

Directly observed treatment (DOT)

DOT is direct observation of the patient taking all drug doses. Historically, it was an essential element of TB control. DOT is still recommended, but varies in practice, and evidence for its efficacy is inconsistent.

- DOT is likely more effective in patients with risk factors for poor adherence, and certain subgroups, e.g. HIV+ve, MDR-TB.
- DOT → improved outcomes when administered by HCWs or trained lay professionals rather than family members; and in community/home-based settings, rather than healthcare settings.
- In addition to DOT, other factors → improved outcomes include patient and staff education, material and psychological support, telephone/SMS communication, and digital medication monitors.
- Video observed therapy (VOT) appears effective in high-income settings and has the potential to supplement/replace DOT.

Pathogenesis

Microbiology

Mycobacteria are slender aerobic bacilli that are 'acid-fast' on Ziehl–Neelsen (ZN) staining. *Mycobacterium tuberculosis* complex comprises *M. tuberculosis, M. africanum*, and *M. bovis*. *M. africanum* behaves clinically and epidemiologically like *M. tuberculosis* and is found mainly in West Africa. *M. bovis* is a pathogen of cattle and other domestic and wild animals, and can also cause TB in humans. All are slow-growing mycobacteria that may require up to 6wks for growth in culture.

Transmission

Individuals with active pulmonary TB (PTB) produce airborne droplet nuclei containing infectious *M. tuberculosis* while coughing, speaking, and sneezing. Infection occurs when these are inhaled by a susceptible person. Crowding, poor ventilation, and duration of exposure ↑ risk of transmission. *M. bovis* can be transmitted by the airborne route, but human infection also occurs through ingestion of unpasteurized milk from infected cows. Transmission may also result from handling TB cultures in the laboratory if appropriate safety equipment and processes are not in place. Other modes of transmission are rare.

TB infection

Aerosolized particles containing *M. tuberculosis* reach alveoli → innate immune response, ingestion by phagocytic cells, and transport to regional lymph nodes (LNs). Here the infection may either be contained, or spread via lymphatics or bloodstream to other organs. Development of specific cell-mediated immunity → lymphocyte cytokine secretion → recruitment and activation of macrophages, which organize into the granulomas characteristic of TB, effectively 'walling in' the bacteria.

In >90% of immunocompetent hosts, the outcome of infection with *M. tuberculosis* is containment of the infection without clinical illness. A fibro-nodular scar at the site of granuloma can sometimes be seen on CXR in the upper lobes (Ghon focus); more commonly, the lesion is not detectable radiographically and a positive TST or TB interferon gamma release assay (IGRA) is the only evidence of infection. *M. tuberculosis* persists intracellularly in a quiescent state within macrophages, retaining the ability to reactivate at a later time, as state known as 'latent TB infection' (LTBI).

Active TB disease

In a minority of adults 1° infection is not contained and progressive 1° TB develops. Disease risk is higher in children, especially in the year following infection. Children <2yrs old and anyone with ↓ cell-mediated immunity are at ↑ risk, esp. for disseminated disease, e.g. miliary TB and TB meningitis (TBM).

Approximately 5–10% of immunocompetent adults with LTBI go on to develop active TB. About half this risk is in the 1st 1–2yrs after infection, the other half is during the remainder of the individual's lifetime. A number of factors including HIV infection ↑ risk of disease reactivation (Box 4.3).

Reinfection with a new strain of *M. tuberculosis* may occur after successful TB treatment, esp. in HIV+ve individuals.

BCG vaccination

BCG is a live attenuated vaccine derived from *M. bovis*. Protective efficacy against active TB ranges from 0% to 80% for reasons which remain controversial. BCG provides some protection against miliary TB and TBM in children. It should be given at birth to all children in high TB prevalence countries (except HIV+ve children, see ➲ Table 22.4, p. 872, and BCG, p. 147). BCG appears to have little or no impact on the overall incidence or transmission of TB in a community.

Box 4.3 Risk factors for development of active TB disease in individuals infected with *M. tuberculosis*

- HIV infection: strongest known risk factor (relative risk (RR) ~20); risk ↓ with ART but remains higher than general population.
- Recent infection: risk of active TB much greater in first 1–2yrs after infection, esp. for children.
- Age: weakened immunity at the extremes of age.
- Malnutrition (body mass index (BMI) <18.5 → RR 2.6).
- Vitamin D deficiency.
- Diabetes mellitus (RR ~2.5).
- Silicosis (RR ~2) and other causes of lung fibrosis.
- Intercurrent infections (e.g. measles, visceral leishmaniasis).
- Alcohol (>40g/day → RR 2.9).
- Active smoking (RR 2.6).
- Indoor pollution (RR 1.5).
- Poverty: probably many biological mechanisms involved.
- Immunosuppression (e.g. corticosteroids, malignancy, anti-TNF therapy).

Clinical features

Diagnostic resources vary widely in different settings. Most TB cases, esp. those with the poorest prognosis and those most infectious to others, can be diagnosed with basic resources, e.g. smear microscopy.

TB in adults

One or more non-specific systemic symptoms are present in most patients: ↓ weight, ↓ appetite, fever, night sweats, or malaise. Other symptoms are related to the site(s) of disease. PTB is the commonest presentation and the most important epidemiologically since it drives transmission. However, TB may affect any organ → a variety of clinical presentations.

Pulmonary TB

Involves lung parenchyma. Cough is common and often productive. Cough for >3wks should always raise suspicion of TB. Other symptoms may include haemoptysis, chest pain, or breathlessness.

Physical examination is often normal or findings non-specific. Some patients look ill and wasted with fever and tachycardia, others may appear surprisingly well (even in the presence of severe CXR findings). There may be localized crackles or signs of pleural effusion on chest examination. Finger clubbing suggests a diagnosis other than TB, e.g. lung cancer, bronchiectasis, or empyema. Occasionally bronchiectasis may be 2° to lung damage from chronic or previous PTB.

Other causes of cavitating lung disease and non-specific symptoms include non-tuberculous mycobacteria (NTM), lung cancer, and fungal lung disease. More rarely, melioidosis (➲ Melioidosis, p. XX) and paragonimiasis (➲ Paragonimiasis, p. XX) may cause a similar presentation in some settings.

Sputum smear +ve PTB (AFB seen in sputum; see Colour Plate 10a.) accounts for ~65% of PTB cases. A positive AFB smear in a high TB prevalence area strongly suggests TB since NTM disease is much less common. Smear +ve patients are most infectious, more likely to have cavities on CXR, and often sickest (mortality is high without treatment). HIV co-infected patients are less likely to have cavities, so less likely than HIV−ve cases to be smear +ve.

Smear −ve PTB remains relatively common in immunocompetent adults, but diagnosis involves a degree of uncertainty unless confirmed by PCR or culture. Many of these patients will become smear +ve if not treated. While underdiagnosis of smear −ve PTB is clearly undesirable, overdiagnosis also creates problems, by misusing the scarce resources of the TB programme, overlooking other treatable diagnoses, and undermining the programme's credibility in the community by ↓ success rate of treatment.

Complications of pulmonary TB

Acute complications include haemoptysis (may be life-threatening) and pneumothorax. Chronic complications include bronchiectasis, lung fibrosis, and aspergillomas (fungus balls) in residual cavities.

Pleural TB

Often unilateral, commonly large, TB pleural effusions can be detected on examination and confirmed by X-ray, USS, and/or diagnostic aspiration. TB effusions are exudates (fluid protein >50% serum protein concentration). Effusions are seldom smear +ve and mycobacterial PCR and culture may be negative (➲ Diagnosis, p. 160). In high-incidence areas, if pleural adenosine deaminase (ADA) is >40U/L with lymphocyte-to-neutrophil ratio of

>0.75, a presumptive diagnosis of pleural TB can be made. In practice, in the absence of explanations such as heart failure, parapneumonic effusion, or malignancy, TB will be the commonest cause of a 'straw-coloured' effusion. Patients with pleural TB may also have involvement of the lung parenchyma on CXR, esp. in HIV co-infection. Hence, sputum smear and culture should be performed. Culture of pleural biopsy tissue may also be helpful and histology of a pleural biopsy usually shows granulomas.

TB lymphadenitis

May involve any site. Cervical LNs are most commonly involved ('scrofula')—esp. right inferior cervical chain as TB bacilli ascend from the paratracheal chain into the right cervical LNs. Lymphadenopathy is typically chronic (weeks–months), and seldom acutely inflamed, distinguishing it from acute viral/bacterial infections. LNs may initially feel rubbery and nontender, becoming matted or fluctuant, and sometimes discharging spontaneously through the skin to produce chronic sinuses with scar formation. TB LNs >3cm in diameter usually contain necrotic areas allowing a little pus to be aspirated. Aspiration of a pointing LN also creates a clean tract that helps prevent scarring. If a large LN is entirely solid, suspect another diagnosis. Paradoxically, TB LNs sometimes enlarge during TB therapy. These characteristics, and the asymmetrical involvement, help to distinguish most cases of TB lymphadenitis from other causes including persistent generalized lymphadenopathy of HIV.

Aspirated LN pus is smear +ve in ~50% cases, esp. in HIV. GeneXpert is ~80% sensitive compared with culture. If negative on needle aspiration, diagnosis can be confirmed by excision biopsy for histology and TB culture (usually a minor procedure in adults). If TB suspected, caseating granulomata on histology are highly suggestive.

Osteomyelitis

Most commonly affects the spine (Pott's disease). All age groups are affected and any level can be involved, although commonly ≥2 adjacent vertebrae at the thoracolumbar junction are infected and in ~30% there is >1 level of spinal involvement.

Anterior vertebral collapse → wedge-shaped vertebra → characteristic kyphosis deformity ('gibbus'). Paravertebral cold abscesses or psoas abscesses may accompany Pott's disease, but usually do not require surgical drainage. The presence of a gibbus in a TB-endemic area is highly suggestive of spinal TB.

MRI is useful if available; CT is second choice; and plain radiographs are often of little help. X-ray signs of intervertebral disc and adjacent bone involvement +/− paravertebral soft tissue densities suggest an infective aetiology but cannot reliably distinguish TB from other infections (e.g. *Brucella*, staphylococci).

If present, a cold abscess can be aspirated; most are smear–ve; some are GeneXpert +ve; culture is most sensitive. Imaging-guided biopsy of the infected disc or adjacent bone requires sophisticated resources.

Spinal TB generally responds well to drug treatment. Rarely patients develop rapidly progressive spinal cord or cauda equina compression, requiring urgent decompression surgery. If surgery is not available, strict bed rest and steroids should be used until the neurological features improve, with gradual steroid withdrawal thereafter. Occasional patients with severe

and unresolving deformities (adults with >60° angulation or children with >30° angulation on X-ray) or chronic neurological compromise benefit from neurosurgery or orthopaedic surgery, if available. With these exceptions, medical therapy alone will result in neurologic improvement or complete recovery in most patients. Spinal deformity will persist, but becomes painless.

TB of other sites (e.g. sternum, hip, knee) generally requires aspiration or biopsy to distinguish TB from other chronic infections.

Miliary TB

An aggressive form of blood-borne TB more common in infants and the immunosuppressed. Typically, the onset is non-specific with progressive fever (sometimes with rigors, which are rare in other forms of TB), malaise, and ↓ weight without a clear identifiable cause. Clinical suspicion is raised by a history of known or likely recent contact with infectious TB. Physical findings are commonly non-specific, but can include hepatomegaly, mild splenomegaly (which is not a feature of other forms of TB), tachypnoea, and wasting.

A CXR (or, preferably, CT scan) demonstrating a diffuse, small nodular infiltrate suggests miliary TB and warrants initiation of TB treatment if the clinical picture is compatible. Sputum smear and TST may be –ve; sputum PCR is usually +ve. If available, biopsy of liver, bone marrow, LNs, or lung parenchyma often yield granulomas and/or AFB. Without prompt treatment, the patient with military TB will inevitably deteriorate and die, often when respiratory distress or TBM occurs.

TB meningitis

More common in children and the immunosuppressed. Onset is often insidious and characterized by progressive fever that may be accompanied by headache, irritability, vomiting, and ↓ consciousness, ultimately → coma. The pace of illness is characteristically slower than in acute bacterial meningitis. Neck stiffness is variable, esp. early in the course. Cranial nerve palsies (particularly VI, also III, IV, VIII) are common, as these nerves run through inflammatory exudate at the base of the brain. Other focal neurological signs may develop as a result of cerebral vasculitis, tuberculomas, or hydrocephalus. Seizures can occur.

Diagnosis rests on CSF examination. Typically, there is ↑ CSF pressure, ↑ CSF white blood count with a lymphocytic predominance, ↑ protein, and ↓ glucose. However not all these abnormalities are present in every case—in particular, neutrophils may predominate early in disease and in HIV co-infection. CSF is rarely AFB smear +ve; mycobacterial culture is +ve in ~80% cases, and GeneXpert in ~50% cases; sensitivity is higher with large volumes (8–10mL) and CSF concentration. Evidence of TB should be sought elsewhere—up to 50% of patients have abnormalities on CXR. In HIV+ve individuals, CSF should also be examined for *Cryptococcus* (➔ Cryptococcal meningitis, p. 112)

A decision to start TB treatment is made on the basis of clinical features, suggestive CSF abnormalities, and the absence of a likely alternative diagnosis, since delay in TBM treatment → poor outcome. Give 2mths intensive phase treatment, followed by 7–10mths continuation phase. Should diagnostic uncertainty exist, repeat LP during observation, or after starting treatment, may be helpful.

Give adjunctive steroids to all HIV–ve patients with TBM (adults >14yrs: dexamethasone IV/PO 0.4mg/kg/24h initially, gradually ↓ over 6–8wks; children: dexamethasone IV/PO 0.6mg/kg/24h or prednisolone PO 4mg/kg/24h for 4wks, then gradually weaned over 4wks). Evidence for steroids in HIV+ve persons with TBM is unclear. Some recommend delaying initiation of ART for 8wks in those with HIV and TBM, due to the risk of IRIS.

Intracranial tuberculomas may accompany TBM or may develop in isolation or as part of disseminated (miliary) TB. Presentations include seizures, focal neurological deficits, and incidental findings on brain imaging. Tuberculomas may also develop or enlarge 'paradoxically' during treatment of these forms of TB. Tuberculomas may require long courses of steroids. Because lesions can persist on brain scans, sometimes with persistent contrast enhancement, TB treatment may need to be prolonged. Treatment duration is usually as for TBM.

Complications of TBM are common and include focal neurological deficits, cognitive impairment, seizures, vasculitis → stroke, ↓ Na due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), tuberculomas, and hydrocephalus. Communicating hydrocephalus is more common in children and may be treated with diuretics and repeated LP; non-communicating hydrocephalus requires ventriculoperitoneal shunt or neurosurgery.

Abdominal TB

Most commonly affects the terminal ileum and peritoneum. Typical symptoms include fever, night sweats, abdominal pain, ↓ weight, abdominal distension, diarrhoea, or partial bowel obstruction. A right lower quadrant 'mass' may be palpable. Ingestion of unpasteurized milk products may suggest *M. bovis* infection, treatment for which is the same as for *M. tuberculosis* (but note that *M. bovis* is intrinsically resistant to pyrazinamide).

Diagnosis is usually made from surgical or endoscopic specimens; histology shows granulomatous inflammation which may be difficult to distinguish from Crohn's disease. Peritoneal TB often develops over time → ascites. Suspect TB if there is ascites without another obvious cause, e.g. cirrhosis. US or CT scans may show thickened terminal ileum, mesenteric LNs, thickened contrast-enhancing peritoneum, and ascites. The ascitic fluid resembles TB pleural fluid (➲ Pleural TB, p. 148). At surgery or laparoscopy, the peritoneum appears covered in white nodules and fibrinous exudate; culture and histology of a peritoneal biopsy are diagnostic.

Pericardial TB

Often initially suspected on the basis of globular enlargement of the cardiac silhouette on CXR in symptomatic patients. Pericardial TB is more common in HIV co-infection. Clinical features of tamponade may be present (↑ jugular venous pressure (JVP), pulsus paradoxus, ↓ BP, muffled heart sounds, ± oedema, hepatomegaly) and a pericardial rub is occasionally audible. USS readily confirms an effusion often with a 'shaggy coat' appearance of the pericardium; later presentations may already have features of pericardial constriction.

Therapeutic pericardial aspiration for tamponade requires USS guidance or at least electrocardiogram (ECG) control. Pericardial fluid is similar to pleural fluid in TB (➲ Pleural TB, p. 148), although often bloodstained. In practice, the diagnosis is often made by on the basis of a pericardial effusion in the absence of other likely causes.

The risk of recurrent tamponade and later pericardial constriction is ↓ by adding corticosteroids to standard TB treatment (starting adult dose prednisolone 60mg/d, gradually weaned over the first 6–12wks of TB treatment). Steroid treatment ↑ risk of malignancy in ART-untreated HIV+ve patients; start ART treatment within 2wks.

Genitourinary TB

Can involve any part of the male or female genitourinary tract. Renal TB may present with dysuria, haematuria, and flank pain or a mass in the flank. Urinalysis typically shows pus cells, but routine culture is –ve ('sterile pyuria'). Diagnosis usually requires TB culture of urine. TB of the uterus or adnexae presents as infertility, pelvic pain or mass, or bleeding. Epididymal swelling is the most common presentation of genital TB in males. Biopsy is usually required to distinguish TB from other possible causes, though imaging (CT scan) may be suggestive of TB.

Diagnosis

Sputum smears

Smear microscopy is the most widely used diagnostic test for TB worldwide, and access to reliable, quality-controlled sputum smear microscopy is a prerequisite for a successful TB programme (Box 4.4). Examine at least two sputum samples from any patient who has a persistent cough lasting for >2wks. Two specimens obtained in the clinic are as sensitive as two samples on separate days. LED fluorescence microscopy is ~10% more sensitive than ZN stain. The concentration of bacteria (scanty to 4+) gives a guide to burden of disease and infectivity of the patient. See Colour Plate 10a.

Nucleic acid amplification tests (NAATs)

Beacon Assays (e.g. GeneXpert MTB/RIF)

GeneXpert MTB/RIF is self-contained, real-time PCR system that automates sample processing and provides a result in <2h, including detection of rifampicin resistance. It does not require a sophisticated laboratory set-up or a highly trained laboratory technician—nurses or other staff can be trained to perform the test. It is recommended as a first-line test although cost, sensitivity to high temperatures, and need for an uninterrupted electricity supply have limited its adoption in some settings.

The MTB/RIF assay is +ve on a single sputum sample in all smear +ve and ~75% smear –ve cases; a second test increases sensitivity by ~10%, a third test by another ~5%. The sensitivity in extrapulmonary samples varies (Table 4.1). Other platforms (e.g. TrueNat and Realtime MTB RIF/INH) show similar sensitivity and specificity to GeneXpert. The Xpert MTB/RIF Ultra has ↑ sensitivity at the cost of ↓ specificity, while a battery operated portable GeneXpert Omni should be useful in 1° healthcare environments.

Line probe assays (e.g. HAIN Genotype MTBDRplus)

Line probe assays test for drug resistance in smear +ve specimens, using PCR and reverse hybridization to detect mutations associated with drug resistance. The most significant advantage is turnaround time (1–2d vs 2–6wks for conventional culture). Cross-contamination and false +ve results may occur, and adequate biosafety, training, and infrastructure are required; they are relatively costly.

Loop-mediated amplification tests

A low-cost, rapid PCR test, recommended as a first-line test for TB. Similar sensitivity/specificity to GeneXpert, but faster to perform, marginally cheaper, and able to be performed at the 1° healthcare level. Manual steps are required and it does not detect drug resistance.

Urine lipoarabinomannan (LAM) lateral flow assay

A direct measurement of a bacterial cell wall component—LAM—in the urine. Particularly helpful in TB patients with advanced HIV (CD4+ <100 cells/mm^3), in whom the test gives additional yield to smear and NAAT techniques, with best results in the sickest patients in whom prompt treatment is most important. Urine is easier to obtain in these patients than sputum. The test can be performed at the bedside in <30mins and is cheap.

Culture

Culture remains the 'gold standard' for diagnosis, and is required for genotyping and detailed drug susceptibility testing. Compared to liquid culture (MGIT, BacT/Alert), solid media (e.g. Lowenstein-Jensen) is cheaper and more robust, but slower (4–6wks vs 2–4wks) and ~10% less sensitive. Sputum is the most common sample; however, specimens from any body site may be cultured. Mycobacterial blood culture may be a particularly useful adjunct to diagnosis but is not validated in standard media. Specifically designed Myco F lytic blood culture bottles have ~15% sensitivity among TB patients overall, and 40% in patients with advanced HIV (CD4+ <150 cells/mm^3).

Chest X-ray

Most useful in patients with chest symptoms who are repeatedly smear –ve, and in identifying pleural effusions, LNs, nodules, and pericardial effusion. A normal CXR does not exclude TB, esp. in HIV. CXR interpretation varies with the skill of the reader and even between skilled readers. However, a CXR alone does not distinguish reliably between TB and other diseases, or between active and past TB. The presence of cavities usually predicts a smear +ve patient who is infectious, but sputum smear is the most reliable predictor of infectiousness.

Box 4.4 Diagnosis of sputum smear −ve TB

Only those with expertise in TB should decide to start treatment for smear –ve PTB. GeneXpert can provide a +ve diagnosis in ~75% of smear –ve, culture +ve PTB cases. Culture and sputum induction ↑ sensitivity of laboratory diagnosis.

Reassessment including repeat sputum examination 2–3wks after a trial of a broad-spectrum antibiotic may clarify the diagnosis. CXR can be helpful. Before diagnosing smear –ve PTB, consider alternatives, e.g.:

- Pneumonia.
- Chronic bronchitis.
- Non-TB respiratory complications of HIV.
- Bronchiectasis.
- Lung abscess.
- Lung cancer.

Tuberculin skin testing

This is a test of immune sensitization by *M. tuberculosis*, which could indicate previous, latent, or active TB—it is not specific for active TB. Following intradermal injection of tuberculin (purified protein derivative), the transverse diameter of skin induration (swelling, not redness) is measured at 48–72h. Training and experience is critical to achieving accurate results. In most situations, ≥10mm is generally regarded as +ve (≥5mm if HIV infected). Both false –ve (normal variation, long time interval since infection, reduced cell-mediated immunity, HIV, old age, severe illness) and false +ve (BCG vaccination, exposure to environmental mycobacteria) TST results are relatively common. The larger the induration, the less likely it is to be a false +ve.

Uses of the TST

- Epidemiologic: determining prevalence or incidence of *M. tuberculosis* infection in a population or group (e.g. HCWs).
- Identification of candidates for treatment of LTBI (e.g. contacts of PTB patients).

Interferon gamma release assays

Using IGRAs to test for latent TB on blood samples is more specific than the TST as they rely on antigens not present in BCG and most environmental mycobacteria. However, IGRAs may be negative in HIV+ve patients, are costly, and their advantage over TST remains controversial.

Serological tests

Multiple commercial tests are available for testing for antibodies in the blood against TB, but they lack sensitivity and specificity, are expensive, and are poorly regulated. They are not recommended.

Table 4.1 Approximate sensitivity of AFB smear, GeneXpert (compared to culture), and culture (compared to clinical diagnosis) in diagnosis of TB

Sample site	AFB smear (vs culture)	GeneXpert (vs culture)	Culture (vs clinical)
Pulmonary	Moderate	High	High
Lymph node	Low	High	Moderate
Pleural	Low	Moderate	Low/moderate
CSF	Low	Moderate/high	Moderate/high
Pericardial	Low	Moderate	Moderate/high

Treatment

Aims of treatment

- To cure the patient and prevent disability.
- To prevent transmission.
- To prevent development of resistant TB.

Principles of anti-TB therapy

- Treatment must always include at least two drugs to which the organism is sensitive.
- *The correct duration:* 6mths for drug-sensitive TB (9–12mths for CNS or spinal TB).
- *Assured adherence:* the TB programme must assist each patient to complete the full course of therapy.

Treatment supervision

As directly observing the patient swallowing each dose by a HCW is not always feasible, a range of alternatives have been tried. Treatment supervisors can incl. teachers, employers, community-chosen volunteers, ex-TB patients, and family members. There must be adequate provision for selection, training, and regular monitoring of the treatment supervisor, a reliable mechanism for delivery of drugs, proper record keeping, and rigorous monitoring of treatment outcomes.

Drug dosage and standard regimen

Table 4.2 Drug dosage and standard regimen

Anti-TB drug	Recommended dose for adults and range (mg/kg)—once-daily regimen
Isoniazid (H)	5 (4–6), max. dose 300mg
Rifampicin (R)	10 (8–12), max. dose 600mg
Pyrazinamide (Z)	25 (20–30), max. dose 2g
Ethambutol (E)	15 (15–20), max. dose 1600mg

Standard TB treatment (Table 4.2 and Boxes 4.5 and 4.6) and duration is effective regardless of disease site, although it is recommended to prolong the consolidation phase for TBM and bone disease (up to 12mths total). TB drugs should ideally be provided in the form of fixed-dose combination (FDC) tablets as this makes monotherapy impossible thereby providing an extra defence against the development of drug resistance. The current rifampicin dose may not be optimal, and higher dose trials are ongoing.

'Retreatment' patients (following loss to follow-up, treatment failure, or relapse) were previously treated using a longer 9mth regimen with the addition of streptomycin for the first 2mths. *This is no longer recommended* due to poor outcomes and ↑ drug resistance. Instead, rapid drug susceptibility testing should be performed and treatment guided by the resistance profile.

Box 4.5 WHO recommended first-line TB regimen

TB drugs and side effects

- Isoniazid (INH; 'H'): potent anti-TB activity. Main serious adverse effect is liver toxicity; can cause peripheral neuropathy.
- Rifampicin (rifampin in North America; 'R'): essential to the success of short-course (<12mths) TB therapy. Important interactions with warfarin, anticonvulsants, oral contraceptives, opiates incl. methadone, nevirapine, efavirenz, and protease inhibitors. Causes orange discolouration of bodily fluids (sweat, urine, tears); liver toxicity.
- Pyrazinamide ('Z'): 'sterilizing' activity allows treatment courses of 6mths. Contribution to first-line regimens limited largely to the first 2mths of therapy. May cause gastritis, hyperuricaemia, and arthralgias; *most hepatotoxic first-line TB drug*.
- Ethambutol ('E'): weak anti-TB agent; main role is prevention of resistance to other drugs. Main serious adverse effect is ocular toxicity, which is uncommon at recommended doses.

First-line regimen (WHO)—2HRZE 4HR

- Isoniazid, rifampicin, pyrazinamide, and ethambutol daily for 2mths 'intensive phase' (2HRZE); followed by 'continuation phase' of isoniazid and rifampicin daily (4HR).
- 3× per week dosing and longer continuation phase regimens are no longer recommended.

Box 4.6 Special groups

- *Isoniazid*: peripheral neuropathy more commonly in diabetic, malnourished, alcoholic, and pregnant patients, and in those with pre-existing neuropathy incl. HIV+ve patients. Give pyridoxine 10–15mg/day to protect against peripheral neuropathy.
- *Women on oral or injectable (hormonal) contraceptives:* must use another form of contraception (e.g. intrauterine contraceptive device, IUD) during rifampicin therapy and for 4–8wks after stopping rifampicin.
- *Pregnancy:* first-line TB drugs may be used in pregnancy. Any theoretical risks to the fetus are much less than the risks from untreated TB.

Monitoring on treatment

Smear +ve patients should have sputum smear examination after 2mths treatment and at least once more before treatment completion. All other patients should be monitored clinically.

Education

Ensure every patient understands that rifampicin discolours the urine and knows the symptoms of drug-induced hepatitis (nausea, vomiting, anorexia, jaundice, dark urine before the daily dose of rifampicin) and to present to a clinic or hospital immediately if jaundice is noted.

Treatment adherence

Good adherence is the most important determinant of cure. As patients feel better ~2mths after starting treatment, motivation to continue therapy wanes. HCWs should support patients to complete TB therapy; the patient and community must be aware of the risks of drug resistance. A good relationship between the patient and clinic staff boosts adherence. Practical measures (e.g. convenient clinic hours for working patients) are very important, as are individualized approaches to patients at risk of defaulting (e.g. help with transportation, nutritional support, addiction treatment, home visits, etc.). Early identification and tracing of defaulters is essential.

Programmatic definitions of treatment outcome

- *Cured*: bacteriologically confirmed TB at start of treatment, smear or culture −ve in the last treatment month and on ≥1 other occasion.
- *Treatment completed*: completed treatment without evidence of failure but no proof of cure (as previously defined).
- *Treatment success*: either cured or completed treatment.
- *Treatment failure*: smear or culture +ve at month 5 or later.
- *Lost to follow-up*: did not start treatment, or treatment was interrupted for 2 consecutive months or more.
- *Died*: any TB patient who died before starting or during treatment.
- *Transfer out*: patient transferred to another unit and whose treatment outcome is unknown.

A similar outcome classification is used for retreatment cases.

Latent TB

Treatment of individuals with latent infection reduces the risk of disease progression/reactivation by ~50%, potentially protecting the health of the individual and the population. LTBI is generally not treated in countries with high TB prevalence currently, as detection and treatment of active disease is the top priority, and a smaller proportion of cases is due to reactivation.

The exceptions are HIV+ve individuals, and children <5yrs old who are household contacts of active PTB cases, and both groups should receive treatment for LTBI.

Contacts of MDR cases should be closely observed and monitored for signs of active TB for ≥2yrs following contact.

Tuberculosis and HIV

HIV suppresses the cell-mediated immune response to TB by CD4+ helper T cells and macrophages. TB incidence ↑↑ in communities severely affected by HIV, and 80% of TB patients in some settings are HIV+ve. Postmortem studies reveal unrecognized TB to be the most frequent cause of death in advanced HIV (~45%).

HIV testing of TB patients: all TB patients should be encouraged to undergo HIV testing. TB programmes should offer HIV testing and coordinate follow-up and support with the HIV programme.

TB testing of HIV patients: assess all HIV+ve individuals starting ART for evidence of active TB, and monitor thereafter.

Preventive therapy of latent TB infection

Preventive therapy ↓ by 60% the risk of developing active TB among HIV+ve individuals who are TST +ve. This benefit extends to those who are TST −ve or IGRA −ve and on ART. Current WHO recommendations are for treatment regardless of TST or IGRA status. The benefits of treatment ↓ over time, esp. if the patient lives in a community where the risk of TB reinfection is high. Care should be taken to exclude active TB, esp. in persons with low CD4+ counts in whom asymptomatic disease may be present, although neither treatment should be delayed unnecessarily.

The usual regimen is isoniazid 300 mg (+ pyridoxine 10 mg) daily for 6mths. Weekly rifapentine–isoniazid for 12wks is a shorter alternative regimen that appears safe with efavirenz- and raltegravir-based ART regimens, has less hepatoxicity and similar efficacy, but is more expensive. In high-income settings, rifampicin/isoniazid for 3mths is often used; however, care is needed with ART interactions.

ART is also very effective in ↓ the risk of TB in HIV+ve individuals by ↑ immune function.

Management of active TB in HIV+ve individuals

Many patients presenting with HIV-related TB do not know their HIV status. Some will have clinical features of HIV infection such as oral candidiasis, chronic diarrhoea, skin and hair changes, peripheral neuropathy, and herpes zoster scars. However, since TB can occur early during the course of HIV disease, clinical features of HIV are often absent.

Extrapulmonary TB is common in HIV, particularly lymphadenopathy, pleural and pericardial effusions, miliary TB, and meningitis. However, PTB, which may coexist with other sites of disease, remains the most common form. The CXR appearance of PTB is often atypical in HIV co-infection, depending on the degree of immune suppression. HIV+ve individuals less commonly have upper lobe disease and cavities and more commonly have non-specific consolidation, intrathoracic adenopathy, effusions, and miliary shadowing.

Persons with advanced HIV and TB often present unwell with sepsis and a corresponding high lactate. The pathophysiology of early mortality in this group is poorly understood and may related to disseminated TB bacteraemia, other nosocomial infections, and poor drug absorption.

Diagnosis

Sputum smear microscopy remains a first-line investigation, see Colour Plate 10a, but is less sensitive in HIV+ve individuals. Where available, GeneXpert testing may be used either alone or alongside smear microscopy. If the smear and GeneXpert are –ve, the differential diagnosis of lung disease in HIV+ve individuals includes the following (see also ➲ Respiratory disease, p. 167):

- Bacterial (most often pneumococcal) pneumonia: a short history and a response to antibiotic therapy are suggestive.
- *Pneumocystis jirovecii* pneumonia (PJP, also called PCP): characteristic features incl. severe dyspnoea, hypoxia, diffuse changes on X-ray, absence of effusions, and response to high-dose co-trimoxazole.
- Pulmonary KS: most patients have cutaneous or oral lesions.

Disseminated TB is more likely in persons with advanced HIV, so consider sampling a wide range of sites, including TB blood culture, urine LAM/culture, LN aspirate or biopsy, pleural and/or pericardial fluid, and CSF. Urinary LAM testing has been associated with ↓ mortality in patients with HIV and symptoms of TB. It is recommended by WHO for HIV+ve patients with CD4 <100 cells/mm³ or who are seriously ill. Patients will often have co-existing pathology alongside TB; investigation and management should reflect this.

In HIV+ve individuals who are unwell, and in whom TB is suspected but initial investigations are −ve, empiric TB treatment may be started. However, attention should be paid to ensuring treatment is completed and all efforts should be made to confirm the diagnosis.

TB treatment regimens in HIV

TB drug treatment regimens are the same for HIV+ve and HIV−ve persons. Cure rates are similar provided the regimen contains rifampicin. Recurrence is more common in HIV, partly due to ↑ reinfection (Box 4.7). In the absence of ART, mortality during and after treatment is ↑↑ among HIV+ve individuals, often due to HIV-related causes other than TB.

ART provision has greatly expanded in resource-poor countries. Treatment with ART and TB treatment presents several challenges which should ideally be managed by a clinician with up-to-date knowledge and expertise in HIV/TB management.

- Adverse TB/ART drug effects may → treatment interruption.
- Complex, clinically important drug interactions, particularly involving rifampicin and PIs.
- IRIS (➲ Immune reconstitution inflammatory syndrome, p. 121).

Treatment initiation

Patients on ART prior to TB diagnosis should continue ART when TB treatment is started, but may require modifications in the ART regimen to ensure compatibility with rifampicin. If not on ART at the time of TB diagnosis, starting TB treatment is the first priority.

Once TB treatment has been started, provide ART regardless of CD4 count. Aim to initiate ART 2wks after starting TB treatment, esp. in patients with low CD4+ counts (<100 cells/mm³), provided the TB treatment is well tolerated. No consensus exists for the timing of ART initiation in CNS TB; however, many experts recommend delaying ART until 8wks after TB treatment started to ↓ risk of CNS IRIS.

An ART regimen consisting of efavirenz or dolutegravir + two nucleoside analogues (ideally emtricitabine/tenofovir; alternative is zidovudine/lamivudine), if otherwise appropriate, is currently the recommended regimen for patients receiving simultaneous ART and TB therapy. In patients on TB treatment, enzyme induction by rifampicin requires twice-daily dosing of dolutegravir.

Alternatives are limited due to drug interactions, particularly with rifampicin (➔ Table 3.5, p. 89). Nevirapine levels are ↓ by rifampicin and potentially ↓ viral suppression. One strategy if using a PI is to replace rifampicin with rifabutin, a costly drug not widely available.

The use of ART regimens consisting of three or four nucleoside analogues largely eliminates concerns about drug interactions, but these regimens appear less efficacious than first-line regimens containing dolutegravir (➔ First-line ART regimens, p. 91).

HIV+ve individuals with MDR TB have a very high mortality rate without ART; there is little information to guide the concomitant use of ART and MDR treatment regimens.

Give prophylaxis (e.g. co-trimoxazole) against other opportunistic infections as for other HIV-infected individuals (➔ Prevention of opportunistic infections, p. 83).

Box 4.7 HIV and TB

Compared to HIV−ve individuals, among TB patients with HIV:

- TB incidence is ↑↑.
- The clinical and radiographic presentation may be different.
- TB treatment is the same and cure rates are similar.
- Recurrence rates and mortality are higher.
- Concomitant ART may complicate TB treatment, but should if possible be started at 2wks, especially if CD4+ <100 cells/mm^3 (ART may be delayed longer in CNS TB).

Tuberculosis in children

Children <2yrs old are more likely than adults to progress to disease following *M. tuberculosis* exposure. Infants who develop TB have a high fatality rate without prompt treatment. By contrast, children aged 7–12yrs have the lowest risk of developing active TB.

Diagnosis of childhood TB is often very difficult, even where culture, X-ray, and other facilities are available (Box 4.8). TB may be suspected clinically in the presence of persistent fever, malaise, and cough. A history of close contact with a smear +ve PTB patient makes TB more likely. A +ve TST or +ve IGRA indicates infection at some time by *M. tuberculosis* and, hence, is supportive, but not diagnostic of TB in a child with an unexplained illness.

Children are less likely to develop pulmonary cavities and may be unable to expectorate sputum, and for these reasons, children with PTB are often sputum smear –ve. A CXR may show enlarged intrathoracic LNs +/− lung consolidation. Bacteriological confirmation may be provided by culture (most sensitive) or GeneXpert PCR of induced sputum, nasopharyngeal aspirates, or gastric lavage specimens. Several scoring systems have been developed to rationalize the diagnosis of childhood TB; none has been validated and they often disagree, but they can guide the puzzled clinician. An example is given in Box 4.9.

Box 4.8 Paediatric TB

- Probably under-recognized.
- High case fatality, particularly in infants.
- Diagnosis commonly difficult and uncertain.

Diagnostic clues: clinical

- History of close contact with smear +ve TB.
- Unexplained fever, unresponsive to other therapy.
- Unexplained, unresponsive weight loss.
- Persistent lymphadenopathy.

Diagnostic clues: laboratory and imaging

- +ve TST and/or IGRA.
- Intrathoracic adenopathy +/− infiltrate on CXR.
- Smear, GeneXpert, or culture (most sensitive) of induced sputum, gastric aspirate, or LN samples.

Box 4.9 Example of a scheme to aid diagnosis of TB in children

1. Score chart for child with suspected TB

Score	0	1	3
Length of illness	<2wks	2–4wks	>4wks
Weight for age	>80%	60–80%	<60%
Family TB (past or present)	None	Reported by family	Known sputum +ve

2. Score for other features if present	
Positive TST	3
Large painless lymph nodes—firm, soft, and/or sinus in neck, axilla, and groin	3
Unexplained fever, night sweats, no response to malaria treatment	2
Malnutrition, not improving after 4wks	3

3. ***If the TOTAL score is 7 or more—treat for TB***

Treat children with a score <7 if CXR is characteristic of TB infection and/or the child does not respond to two 7d courses of two different antibiotics.

Multidrug-resistant and extensively drug-resistant tuberculosis

A key responsibility of a TB programme is to prevent TB bacilli from becoming resistant. *Acquired* drug resistance requires two steps:

- A random mutation of the TB bacillus conferring drug resistance.
- Followed by selection 'pressure' from the use of that drug.

Resistant organisms replicate more rapidly in the presence of the drug, unless suppressed by another drug. They may then be transmitted to other people (*transmitted* drug resistance).

Definitions

Multidrug resistant (MDR)-TB implies resistance to isoniazid and rifampicin. Rifampicin-resistant TB should be treated the same as MDR-TB.

Extensively drug resistant (XDR)-TB is MDR plus resistance to any fluoroquinolone and at least one additional Group A drug (see Box 4.1).

Pre-XDR TB, is MDR plus resistance to any fluoroquinolone.

Totally drug-resistant (TDR-) TB is resistance to all first- and second-line drugs.

Epidemiology

Approximately 5% of TB patients worldwide have MDR-TB. Among retreatment cases the proportion of MDR cases is ~20%. Of those with MDR, ~10% have XDR TB. The MDR-TB burden is highest in settings where TB programmes have been weak historically—China, India, the former Soviet Union, and Eastern Europe. Previous failure to complete treatment remains the major risk factor, but as many as 50% may be transmission cases. Vigilance in MDR-TB contacts is very important.

Diagnosis

Standard culture confirmation of MDR-TB takes weeks to months and requires complex and costly laboratory resources. Non-commercial direct phenotypic assays are quicker and cheaper (e.g. microscopic observation drug susceptibility (MODS) or nitrase reductase assays). Molecular tests offer quickest turn-around times. In high-incidence MDR-TB settings, rifampicin resistance detected by GeneXpert predicts MDR-TB, although false +ves may occur. Line probe assays for first- and second-line drug resistance can be used on smear +ve and cultured samples.

Management

This is a complex and changing area, thus it is essential to check with local and/or WHO guidelines before deciding on a regimen. New TB drugs (e.g. bedaquiline, delamanid), better regimens, and programmatic improvements have ↑ cure rates from ~60% to ~80%. In 2019, WHO published new treatment guidelines on drug-resistant TB (http://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/). These include a shorter 9–12mth regimen that may be used in selected patients with low risk of XDR-TB; and a longer 18–20mth regimen.

Shorter standardized regimen

- Consider if not pregnant and no other contraindications (Box 4.10).
- 4–6mth intensive phase of seven drugs (varies, but typically: amikacin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol) followed by 5mths moxifloxacin, clofazimine, pyrazinamide, and ethambutol.
- For uncomplicated disease, in settings where pre-XDR TB has been excluded with TB rapid drug susceptibility, an oral regime may be used, by swapping amikacin for bedaquiline.
- ↓ costs, ↑ completion and cure rates, and ↑ patient retention.

Box 4.10 Contraindications to shorter MDR-TB regimen

- Confirmed resistance to/suspected ineffectiveness of a medicine in the shorter MDR-TB regimen (except isoniazid resistance).
- Exposure for >1mth to any second-line medicines in the shorter MDR-TB regimen (unless drug susceptibility is confirmed).
- Drug intolerance or risk of toxicity (e.g. drug interactions).
- Disseminated, meningeal, or CNS TB (any extrapulmonary TB in HIV).

Longer individualized 18–20-month regimen

- Regimen should be individualized to comprise at least four drugs likely to be effective—ideally including three group A agents and at least one group B agent (Table 4.3); group C drugs are added when drugs from groups A/B cannot be used. Bedaquiline is stopped after 6mths.
- For the first time this provides a fully oral regimen in many cases.

Monitoring during treatment is complex as the therapeutic margins are narrow, toxic side effects are common (Table 4.3), and regimen changes are often required. Given its complexity and expense, treatment should ideally be under the national MDR-TB programme with close reference to WHO, national, and local guidelines, and supervised by a clinician with expertise in MDR-TB. Regardless of drug treatment, it is important to prevent acquired resistance and healthcare-associated transmission.

Table 4.3 Drugs in MDR-TB regimens and common side effects

Group A	Levofloxacin *or* moxifloxacin	QTc prolongation
	Bedaquiline	QTc prolongation
	Linezolid	Myelosuppression; optic/peripheral neuropathy
Group B	Clofazimine	QTc prolongation
	Cycloserine *or* terizidone	Neuropsychiatric symptoms, ↓ seizure threshold
Group C *(in ↓ order of usual preference)*	Ethambutol	QTc prolongation (if ↓ albumin)
	Delamanid	Hepatotoxicity
	Pyrazinamide	*(Usually given with Co-amoxiclav to potentiate action)*
	Imipenem *or* meropenem	
	Amikacin *or* streptomycin	Ototoxicity/nephrotoxicity
	Ethionamide *or* prothionamide	Hypothyroidism
	Para-aminosalicylic acid	Hypothyroidism

Chapter 5

Chest medicine

Stephen Graham

Symptoms of respiratory disease

Cough

Acute cough without evidence of respiratory distress, e.g. fast or difficult breathing, or serious systemic symptoms, usually requires no investigation or treatment. Persistent cough (>2–3wks) associated with phlegm, fever, weight loss, dyspnoea, haemoptysis, or chest pain needs investigation. Nocturnal coughing is a feature of asthma (spirometry helpful), left ventricular failure (LVF), tropical pulmonary eosinophilia (TPE), and gastro-oesophageal reflux disease (GORD). Most causes of cough can be diagnosed by a careful history, physical examination, a blood count, and a CXR.

Common causes of cough

Acute

- Viral upper (URTI) or lower respiratory infection (LRTI).
- Pneumonia.
- Inhaled foreign body (esp. in children).
- Acute sinusitis.

Chronic

- Asthma (can be without wheezing).
- Pulmonary TB, incl. intrathoracic lymph node enlargement.
- GORD—usually non-productive.
- Chronic bronchitis including chronic obstructive pulmonary disease (COPD).
- Bronchiectasis.
- Chronic sinusitis, with a post-nasal drip.
- Drugs—ACE inhibitors and beta blockers.

Uncommon causes of cough

- Larva migrans (*Ascaris*, *Strongyloides*).
- TPE.
- Pleural effusion.

Haemoptysis

Severe haemoptysis is an emergency—maintain a clear airway, as patients die of asphyxiation (blood or clot in trachea) or aspiration rather than exsanguination. A careful history is needed to differentiate haemoptysis from haematemesis, oropharyngeal bleeding, or posterior epistaxis; sometimes needs to be witnessed. Patients should be closely observed and investigated. Patients with haemoptysis will continue to expectorate blood for 24h after the acute event.

Common causes of haemoptysis

- Infections: TB, acute LRTI, acute bronchitis.
- Neoplastic: carcinoma of bronchus.
- Cardiovascular: mitral stenosis, pulmonary embolism (PE) (with infarction).
- Pulmonary disease: bronchiectasis.

Other causes of haemoptysis

- Infections: lung abscess, parasitic disease (e.g. paragonimiasis), fungal disease (e.g. aspergillosis), pleuro-pulmonary amoebiasis.
- Trauma: lung contusions, foreign body aspiration, post-endotracheal intubation, or following aggressive endotracheal suctioning.
- Diffuse pulmonary parenchymal disease: Goodpasture's syndrome, granulomatosis with polyangiitis (formerly Wegener's granulomatosis), systemic vasculitides.
- Cardiovascular: pulmonary oedema, pulmonary hypertension, aortic aneurysm.
- Bleeding tendency: sepsis, DIC, snake bite, haemorrhagic fevers.

Dyspnoea/breathlessness

Breathlessness can be due to respiratory, cardiac, or haematological causes (or combinations). Look for anaemia, wheezing (may have both pulmonary and cardiac causes), signs of LVF, and note the pattern of breathing. Acidosis is associated with sighing breathing (Kussmaul) and the breath may smell (ketones). Usually, clinical examination, CXR, ECG, and blood count will guide appropriate treatment. In patients with COPD, type 2 respiratory failure may → CO_2 retention—do blood gas measurements for optimal management (➲ Chronic obstructive pulmonary disease, p. 212).

Diagnosis

- *Pulmonary*: often associated with tachypnoea, ↑ respiratory effort, wheezing, or chest pain. Consider pneumothorax, PE, pneumonia, and pleural effusions, as well as asthma, COPD, interstitial lung disease (ILD), pulmonary fibrosis, and pulmonary hypertension.
- *Cardiac*: often with paroxysmal nocturnal dyspnoea, orthopnoea, or ankle oedema—inability to lie flat is a crucial observation. Examination for ↑ JVP and swelling of ankles is essential. Cor pulmonale is common, along with LVF due to valvular or ischaemic heart disease or myocardial disease due to myocarditis or cardiomyopathy.
- *Diseases of the chest wall (rare)*: severe kyphoscoliosis, GBS, neurotoxic snake envenoming, myasthenia gravis, and ankylosing spondylitis.
- *Anaemia*: if acute, or chronic and severe.

Wheeze

Wheezes are (generally expiratory) musical sounds coming from the lower airways. Wheezes may vary in pitch and intensity and can be heard at the mouth in some patients. Localized wheeze may be due to partial endobronchial obstruction.

Causes of wheeze

- Lower airways obstruction, especially asthma and COPD.
- Infection, especially *Mycoplasma pneumoniae* and rarely, parasitic disease—Katayama fever in schistosomiasis, ruptured hydatid cyst.
- LVF—peribronchial oedema causes bronchospasm.
- Inhalation of toxic chemicals or smoke.
- Endobronchial obstruction from a tumour or foreign body (localized wheeze).

  Multiple causes of a wheeze may exist in a single patient.

  In children consider previously listed causes, but also:
- Bronchiolitis (usually <2yrs, commonest <1yr).
- Viral-induced wheeze (related to concurrent URTI).

Stridor

Stridor is less common, especially in adults. It is a harsh sound heard in inspiration, due to obstruction of the trachea or larynx. If severe, it is also heard in expiration. Stridor is more common in children, due to the susceptibility of the upper airways to obstruction from inflammation.

Acute

- Foreign body.
- Infections: viral croup (➲ Acute laryngotracheobronchitis: croup, p. 188), bacterial tracheitis (➲ Bacterial tracheitis, p. 190), diphtheria (➲ Diphtheria, p. 194), epiglottitis (➲ Paediatric acute respiratory infections: epiglottitis, p. 186), and retropharyngeal abscess.

Chronic

- Tumour.
- Retrosternal goitre.
- Laryngomalacia (in infancy: usually resolves with time).

Pneumonia

Pneumonia is the leading cause of child deaths globally, accounting for >800,000 child deaths (<5yrs) in 2017, with highest incidence and mortality in resource-poor regions. It affects adults esp. the elderly and HIV+ve individuals. Most serious cases are bacterial, although it can occur as part of a severe systemic viral infection (esp. measles or influenza).

Epidemiology

The incidence, aetiology, and clinical severity of pneumonia depends on the patient's age (Table 5.1), and the presence of other comorbidities. *Streptococcus pneumoniae* (pneumococcus) is the most common cause of bacterial pneumonia at all ages, hence the worldwide drive for pneumococcal vaccination (➲ Pneumococcal vaccines, p. 852). Bacteria cause 25–50% of severe pneumonia cases in children, being commonest in communities with poor living conditions. Viruses also commonly cause pneumonia in infants and children worldwide.

In order to determine the likely cause of pneumonia and severity (Table 5.2), consider age, immunization status, and the following:

Table 5.1 Organisms common in particular age groups

Age	Organism
Neonates	Gram +ve organisms (group A *Streptococcus*, group B *Streptococcus*, *Streptococcus pneumoniae, Staphylococcus aureus*)
	Gram –ve organisms (*Escherichia coli*, *Salmonella* sp., *Klebsiella*)
	Less common: *Chlamydia*, *Listeria*, *Bordetella pertussis*
<5yrs	*Streptococcus pneumoniae*
	Haemophilus influenzae
	Group A *Streptococcus*
	Staphylococcus aureus (severe), especially post measles infection
	Bordetella pertussis
	Viral: respiratory syncytial virus (RSV), human metapneumovirus, measles, influenza, adenovirus, parainfluenza
School age	*Streptococcus pneumoniae*
	Mycoplasma, *Chlamydia*
	Viral pneumonias as above-listed
Adults	*Streptococcus pneumoniae*
	'Atypical' organisms (*Mycoplasma*, *Chlamydia*, *Legionella*)
	Haemophilus influenzae
	Viral pneumonias: influenza, adenovirus, varicella zoster

Was infection acquired in the community or hospital?

- In a previously healthy person with community-acquired pneumonia (CAP):
  S. *pneumoniae* is most likely bacterial cause.
  - Respiratory viruses are common causes, and 2° bacterial infection can occur.
  - Atypical organisms are implicated less often.
  - TB is a possibility, especially if response to antibiotics is poor.
- In hospital-acquired (nosocomial) pneumonia, Gram –ve infections and antibiotic resistance are common, so treat with broader-spectrum antibiotics (➲ Management of pneumonia: adults, p. 180).

Are risk factors for disease present?

- Malnutrition.
- HIV+ve.
- Asplenia/hyposplenism (e.g. due to sickle cell disease).
- Chronic lung disease.
- Diabetes.
- Cerebral palsy.
- Immune deficiency (e.g. hypogammaglobinaemia).
- Alcoholism or IV drug use.
- Poor dental/gingival hygiene.

Some risk factors are associated with particular organisms

- Chronic lung disease → colonization, e.g. with *Haemophilus influenzae*.
- Alcoholism or IV drug use → Gram –ve bacterial infection, ↑ risk TB, pneumococcal infection, and aspiration pneumonia.
- ↓ consciousness (e.g. head injuries or epilepsy) and children with cerebral palsy have ↑ risk of aspiration pneumonia.
- Poor dental hygiene → anaerobic infection from oral or gum flora → pneumonia which often → lung abscess (➲ Lung abscess, p. 204).

Table 5.2 Markers of severity

Clinical features	Investigations
Confusion/sepsis	Blood urea >7mmol/L
Respiratory rate >30/min	WCC <4 × 10^9/L or >30 × 10^9/L
Diastolic BP <60mmHg	Arterial PO_2 <8kPA
New atrial fibrillation	Serum albumin <25g/L
	Multilobe involvement

Clinical features: adults

- Systemically unwell with malaise, fever, anorexia, body aches, and headache, may have delirium if severe.
- ↑ RR and respiratory signs incl. cough, sputum production, dyspnoea, pleural pain, and, rarely, haemoptysis.
- In lobar pneumonia, chest movements may be ↓ on the affected side; ↓ percussion note, ↑ vocal resonance/fremitus, bronchial breathing, inspiratory crackles, and pleural rub may be present on auscultation. After

a few days, an effusion often occurs, changing the clinical signs. Sputum is often initially scanty or absent → purulent or blood-streaked later.
- Lower lobe pneumonia with diaphragmatic pleurisy may mimic an acute abdomen—abdominal pain, ileus, rigidity.
- In the elderly or debilitated, bronchopneumonia rather than lobar pneumonia is common, so there may be fewer signs. Look for ↑ RR and perform a careful chest examination.

A poor prognosis is associated with
- Bacteraemia (e.g. the fatality rate ↑ from 5% in isolated *S. pneumoniae* pneumonia to 25–35% if bacteraemic).
- Infections with *S. aureus, H. influenzae* type B, and Gram –ve bacteria.
- Previous illness, either chronic (e.g. COPD, cardiac disease, HIV+ve, malnutrition) or acute (influenza, measles).

Common pathogens in CAP have particular clinical features which may be helpful.

Streptococcus pneumoniae

URTI → sudden-onset fever, rigors, malaise, headache, myalgia. At extremes of age, onset is often less clear, children show ↑ RR in addition to fever and cough, elderly may have little fever and present with confusion. Chest pain (pleuritic, sometimes referred to shoulder if diaphragm is involved) and cough (initially painful and dry → blood-tinged → purulent) commonly follow. Lower lobe involvement can result in abdominal pain and guarding. WCC is often ↑.

Pneumococcal conjugate vaccine reduces incidence due to vaccine serotypes and is increasingly available in high-incidence settings.

Haemophilus influenzae type B (Hib)

Occurs in children <5yrs old, with lobar pneumonia, pleural involvement, and effusion. Also in adults as a 1° infection or in previously damaged lungs. Onset may be slow and accompanied by infection elsewhere (e.g. meninges, epiglottis). Hib vaccine has ↓ incidence dramatically.

Staphylococcus aureus

Affects patients with pre-existing lung disease, especially following viral infections, such as influenza or measles. Influenza infection may be subclinical. Alternatively, haematogenous spread from a distant site (e.g. skin, bones and joints, or heart) may produce pneumonia in a previously healthy lung and *S. aureus* may be isolated from blood. It is always a serious condition with high fever and cyanosis; common complications include pulmonary abscess formation, cavitation, and empyema.

Clinical features: children

- Symptoms: systemically unwell, fever, cough, difficulty breathing.
- Non-specific symptoms such as abdominal pain, vomiting, and refusal of feeds may be the only symptoms.
- Signs of respiratory distress: ↑ RR (note: age dependent—see Box 5.1 and Table 5.3), nasal flaring, lower chest wall in drawing, tracheal tug, head-nodding, grunting, or nasal flaring.
- Signs such as bronchial breathing, crackles, and pleural rub are less common. Absence of sputum is common.

WHO classifies pneumonia in children (as pneumonia or severe pneumonia, see Box 5.1) according to the presence of specific signs and symptoms. A poor prognosis is associated with:

- Presence of bacteraemia or clinical signs of shock or sepsis.
- Hypoxia and other signs of severe pneumonia.
- HIV infection and/or severe malnutrition.

Table 5.3 Respiratory rates in children of different ages: count RR for 1min in calm circumstances—crying gives a falsely ↑ RR

Age	Normal RR/min	Tachypnoea or fast breathing
<2mths	40–30	>60
2–11mths	40–30	>50
12mths–5yrs	30–25	>40
>5yrs	25–20	>30

Box 5.1 WHO classification of pneumonia in children

Severe pneumonia

Cough or difficulty in breathing, plus at least one of the following: central cyanosis or O_2 sats <90%, severe respiratory distress (e.g. grunting, very severe chest indrawing), presence of a general danger sign (inability to breastfeed or drink), lethargy/unconsciousness/convulsions or clinical signs such as bronchial breath sounds, and/or signs of pleural effusion/empyema. Other signs of pneumonia, as follows, may also be present.

Pneumonia

Cough or difficult breathing with at least one of fast breathing (as per Table 5.3) or lower chest wall indrawing. They may also have signs of pneumonia on auscultation such as crackles, or pleural rub.

Atypical pneumonia

'Atypical' organisms cause <10% of all pneumonias in LMICs; consider TB in cases of non-resolving chest infection. In HIV+ve individuals, mixed infections are common. PCP is a common cause of severe pneumonia in HIV+ve infants not receiving ART, with or without CMV co-infection (➲ Respiratory disease, p. 175).

- Atypical pneumonias include; *Mycoplasma pneumonia*, *Chlamydia pneumoniae*, *C. trachomatis*, *C. psittaci*, *Coxiella burnetti*, *Legionella pneumophila* (➲ Legionnaires' disease, p. 175), and viruses (e.g. influenza and adenovirus).
- Organisms are difficult to culture and diagnosis is clinical, supported by CXR, blood picture, serology, or nasopharyngeal aspirate (if available).
- Atypical pneumonia affects previously healthy individuals of all ages.
- Symptoms are dyspnoea, dry cough, fever, and malaise.
- Chest signs are uncommon.
- CXR often shows bilateral, fluffy infiltrates, and appears worse than the clinical signs suggest.
- Treatment with doxycycline or macrolide; if severe → ICU admission.

Legionnaires' disease

The importance of *Legionella pneumophila* in the tropics is unknown. It is transmitted by inhalation of aerosolized water droplets from air conditioning, water tanks, showerheads, and medical equipment (e.g. nebulizers).

Clinical features

Vary from subclinical or mild infections to severe pneumonia. In severe infection, after 2–10d, there is abrupt high fever, rigors, myalgia, and headache → dry cough, dyspnoea, and crackles. Patient appears toxic, sometimes with delirium or diarrhoea. Complications incl. respiratory failure, pericarditis, myocarditis, and AKI.

Diagnosis

Gram –ve slender rods of variable length in biopsy or sputum samples; bacterial antigen in urine for first 1–3wks.

Management

Erythromycin 0.5–1g/6h IV or oral (+/– rifampicin 600mg bd, moxifloxacin 400mg od, or ciprofloxacin 500mg bd) for 2–3wks. Exclude TB if rifampicin or quinolones used, as these have potent anti-TB activity.

Prevention

Maintenance of stored water and tanks to prevent bacterial colonization and spread.

Recurrent pneumonia

The occurrence of more than two episodes of pneumonia may be caused by:

- Respiratory disease: COPD, bronchiectasis, bronchial obstruction (foreign body, bronchial carcinoma, lymphadenopathy, bronchial stenosis), and intrapulmonary sequestration.
- Non-respiratory, e.g. recurrent aspiration, immunosuppression, and HIV.

Nosocomial pneumonia

Definition Pneumonia >48h after admission to hospital. An increasing problem in sub-Saharan Africa, with a high case fatality risk in children admitted to hospital.

Aetiology Aspiration of nasopharyngeal secretions, inhalation of bacteria from contaminated instruments, haematogenous spread (e.g. from abdominal infection, infected cannulae, or catheters left in for too long).

Risk factors Malnutrition, low birth weight, elderly, smoking, long preoperative stay, prolonged anaesthesia, intubation, abdominal/thoracic operations, plus risk factors for aspiration pneumonia (➔ Aspiration pneumonia p. 177).

Clinical features Development of fever, cough.

Diagnosis ↑ WCC, purulent sputum, lung infiltrate on CXR.

Management Chest physiotherapy postoperatively may help ↓ nosocomial pneumonia. IV antibiotics (➔ Management of pneumonia: adults, p. 178).

Prevention Infection control measures in hospitals incl. hand washing. Prevent smoking preoperatively, good respiratory equipment hygiene.

Aspiration pneumonia

Risk factors

↓ consciousness (e.g. epilepsy, excess alcohol), dysphagia, immobility, neuromuscular diseases, and inability to clear bronchial secretions or cough after surgery. In children, also consider GORD, esp. if underlying neurological/neuromuscular disorders.

Aetiology

- In the community: anaerobes from oropharynx and teeth crevices (normally penicillin sensitive).
- In hospital: aerobic bacteria become more important, esp. Gram –ve enterobacteria and *Pseudomonas aeruginosa*.

Anaerobic infection suggested by poor dental hygiene, aspiration, or ↓ consciousness. As the infection proceeds, tissue necrosis → foul-smelling purulent sputum.

Management of pneumonia: adults

Treatment

Follow local antimicrobial guidelines if available—or use empiric treatment (Table 5.4).

Supportive care

- Oxygen: if ↑ RR measure O_2 sats and provide O_2 (usually by concentrator at 4 L/min). In extreme hypoxia, two concentrators can be used (one by nasal cannulae, the other by mask). If concentrators are scarce, the supply can be split to two patients.
- Analgesia if pleuritic pain.
- Fluids (IV if necessary): treat dehydration and maintain adequate urine output (>1mL/kg/h). Losses ↑ if the patient is febrile. SIADH is common in severe pneumonia.
- Rest: the patient should sit up, rather than lie flat.
- Physiotherapy not recommended in acute pneumonia; useful when pleuritic pain has subsided.

Antimicrobial use: general points

- Obtain culture specimens if microbiological facilities available, then immediately begin empirical antibiotics, following local guidelines. Give IV therapy if the patient is very ill, cannot swallow/vomits, or if GI tract is not functioning.
- Give antibiotics for 3–7d in non-severe pneumonia. For severe pneumonia, continue treatment according to the clinical response. In the presence of cavitation and abscess, treat for 3–4wks.
- *Streptococcus pneumoniae* has progressively become ↓ sensitive to penicillin: >50% of pneumococcal isolates in some countries have ↓ laboratory sensitivity to penicillin, but this is of limited significance except in meningitis. Treat with high-dose penicillin unless local guidelines indicate otherwise.
- Nosocomial infections include Gram –ve organisms and require broad-spectrum antibiotics.
- Aspiration pneumonia includes anaerobes, use: cephalosporin + metronidazole, or penicillin + aminoglycoside + metronidazole.

Chest X-rays in pneumonia

The value of CXR for each patient should be carefully considered:

- Is the diagnosis already clear from the clinical features? Typical pneumococcal pneumonia need not be X-rayed.
- Cavitation on CXR widens the diagnosis to include TB, *Staphylococcus aureus*, *Klebsiella*, melioidosis, or paragonimiasis.

Note: CXR changes in pneumonia may take 3mths to resolve following successful treatment and clinical improvement by the patient.

Complications

Pneumococcal pneumonia often → complications if poorly treated. A reactive effusion may be present → complicated parapneumonic effusion → empyema (Empyema, p. 197). Haematogenous spread can → infection of meninges, joints, eyes, or abscess formation in distant organs. Rare complications incl.: septicaemia in patients with underlying conditions, such as asplenia; endocarditis; and peritonitis in patients with ascites.

Prevention

Protein-conjugate vaccines prevent disease from vaccine serotypes of pneumococcus and *Haemophilus* (➲ *Haemophilus influenzae* type b (Hib) vaccine, p. 851) in children and HIV+ve individuals. Pneumonia should prompt an HIV test. Smoking is a contributing cause of pneumonia.

Table 5.4 Empiric treatment of pneumonia

Clinical picture	Likely organisms	Antibiotic route	
		Oral	IV
Community-acquired pneumonia			
Mild to moderate	S. *pneumoniae*	Ax	A or Ax
If 'atypical'		Add E	
2° pneumonia			
Previous lung disease (e.g. COPD)	S. *pneumoniae* *H. influenzae*	CoAx or C	CoAx or C
If following flu, measles or URTI	S. *aureus*	Add F to above regimen	
Aspiration	S. *pneumoniae*, *Klebsiella* spp., anaerobes, Gram −ve organisms	CoAx	P.. + G
Immunosuppression (e.g. leukaemia)	*Pseudomonas* spp.		Cz + G
Nosocomial (especially if 2° disease)	Gram −ve		Ct + G
Sepsis elsewhere	Treat as for sepsis		F.. + M
Severe pneumonia	Widest possible range		Ct + E + G
Cavitation	TB, *Klebsiella* (South Africa), melioidosis (Southeast Asia), *S. aureus*		

Key to antimicrobials (dose indicated is for adults):

A Ampicillin 500mg qds IV.

Ax Amoxicillin 500mg tds oral or IV.

C Cefuroxime 750mg tds IV or 500mg bd oral.

CoAx Co-amoxiclav 1 tablet (500mg/125mg) tds oral or 1.2g (1000mg/200mg) tds IV.

Ct Ceftriaxone 1–2g IV or cefotaxime 1g tds IV.

Cz Ceftazidime 2g tds IV.

E Erythromycin 500mg qds oral or 500mg qds slowly IV.

F Flucloxacillin 500mg qds oral or 250–1000mg qds slowly IV.

G Gentamicin 3–5mg/kg od IV.

M Metronidazole 500mg po tds (for up to 7d).

P Benzylpenicillin 1.2–1.8g qds IV (dose may be increased).

A, Ax, and oral CoAx doses can be doubled in severe infections; the IV CoAx dose can be increased in frequency to qds.

Viral pneumonia (SARS and H1N1)

In 2002–2003, an unusual coronavirus caused a large number of cases of a severe acute respiratory syndrome (SARS) with a high morbidity and mortality and spread rapidly across continents from its origin in China. In 2009–2010, an influenza A (H1N1) outbreak in Mexico initially had a high mortality in young adults and became a global pandemic. In other regions the severity was similar to seasonal 'flu, but with a younger age distribution. Zoonotic viral outbreaks will continue to be important globally. Influenza, parainfluenza, RSV, human metapneumovirus, and adenovirus can all cause viral pneumonia in children and adults, esp. those with chronic disease.

Clinical features

Fever, cough, malaise, diarrhoea, myalgias, and headache occur after an incubation period of 2–7d. In many patients CXR shows infiltrates and patchy consolidation esp. in the lower zones. As the illness progresses, CXR shadowing worsens → development of ARDS and multiorgan failure. Recovery may be slow and some patients develop pulmonary fibrosis. Diagnosis is based on the clinical sequence of events during an outbreak. Cultures of viruses are not possible in routine laboratories and a reverse transcription PCR diagnostic test in a surveillance laboratory (where available) should be requested on initial cases using blood, urine, and nasopharyngeal samples.

Management

Specific antiviral therapy is of value if started early in the course of the illness. Steroids have been tried in SARS, but no benefit has been found; their role in influenza is unclear. Supportive treatment in an ICU may be required. 2° bacterial infection contributed to mortality in the H1N1 pandemic (2009–2010), and staphylococcal pneumonia also ↑ in incidence following influenza infection.

COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified as a cause of epidemic pneumonia in China in December 2019. Coronavirus disease 2019 (COVID-19) has since become a global pandemic with major health, social, political, and economic consequences. COVID-19 epidemiology and management continue rapidly to evolve, aided by unprecedented collaboration and progress on research. Please refer to current guidelines for the most up-to-date information.

Epidemiology

The global burden is summarized at https://coronavirus.jhu.edu/map. At the time of writing there have been over 120 million cases and nearly 3 million deaths documented worldwide. These figures may underestimate the true burden due to limited case ascertainment in some settings.

Transmission may occur via the following routes:

- *Direct droplet transmission* due to coughing, sneezing, breathing close to someone: mediated by larger respiratory droplets that settle within 1–2m; thought to be the major route of transmission.
- *Indirect droplet transmission* due to transfer of infectious droplets via surfaces (fomites); contribution to transmission currently uncertain.
- *Airborne transmission* due to infective microdroplets suspended in the air; contribution to community transmission currently uncertain; important in context of *aerosol-generating procedures* e.g. respiratory tract suctioning, high-flow nasal oxygen (HFNO), non-invasive ventilation (NIV), intubation and mechanical ventilation, bronchoscopy, etc.

The incubation period is 2–14d (median 5d). Viable virus is shed from 1–2d before and up to 10d post symptom onset sometimes longer in the immunosuppressed. Dead virus may be detectable by PCR several weeks after infection. Symptomatic individuals are most infectious; measures to limit symptomatic transmission ↑ the relative contribution of presymptomatic and asymptomatic cases to community transmission.

Pathology

Severe disease is characterized by high VLs and diffuse alveolar damage in the initial phase, followed by an immune-mediated phase with multiorgan involvement, endothelial injury, and thrombosis.

Clinical features

Clinical spectrum ranges from asymptomatic infection to severe disease and death. Common symptoms include fever, myalgia, cough, breathlessness, loss of taste and smell; 5% present with GI symptoms. Presentation in elderly/vulnerable may be non-specific, e.g. delirium, functional decline.

Severe illness frequently biphasic with acute and often rapid deterioration in week 2, likely due to immunopathology. Deterioration often heralded by severe hypoxia which may be surprisingly well tolerated initially, but is an indication for urgent admission, investigation, and treatment.

Multisystem involvement may resemble other causes of sepsis, with marked inflammation, fever, and multiorgan failure. Vascular involvement → venous and sometimes arterial thromboembolism.

Investigations and diagnosis

Suspect if compatible symptoms and known community transmission.
Rapidly assess vital signs including oxygen saturation (SaO_2); continue frequent monitoring.
Bloods incl. FBC, U&E, CRP, LFT, D-dimer +/− blood cultures.
CXR/CT may show patchy bilateral peripheral ('ground-glass') opacities.
Low threshold for investigating and treating for DVT/PE.

Virological diagnosis

Nasopharyngeal swab or BAL for SARS-CoV-2 PCR: sensitivity highest (up to >90%) in the first week of illness.
Rapid antigen tests are less sensitive but detect the most infectious cases.
Serology usually positive by day 14, but wanes over time.

Treatment

Supportive

- Give O_2 to keep SaO_2 ≥92-96% (≥88% if risk of type 2 respiratory failure).
- HFNO / NIV +/− proning may avoid need for mechanical ventilation in progressive respiratory failure, but do not delay intubation if continued deterioration despite HFNO/NIV and treatment escalation appropriate.
- Other organ support (e.g. renal replacement therapy, as required).
- Treat with antibiotics if 2° bacterial pneumonia suspected.
- Give prophylactic low-molecular-weight heparin to all hospitalized patients.

Specific therapy

- Corticosteroids ↑ survival in patients requiring O_2 (avoid if not hypoxic as trend towards harm). Give dexamethasone 6mg od PO/IV or hydrocortisone 50mg qds IV or prednisolone 40mg od PO. Continue for 7–10d or until discharge if sooner. Monitor blood glucose.
- The antiviral remdesivir shortens time to recovery and may help prevent progression to more severe respiratory failure.
- If available, Tocilizumab ↓ mortality in hospitalized patients.
- Only use other investigative treatments in a clinical trial until there is evidence of benefit.

Prognosis

In-hospital mortality varies from 20% to 65% depending on population risk factors and medical resources. Older age is the strongest risk factor for death; others are male sex; non-white ethnicity; chronic cardiac, respiratory, renal, and liver disease; diabetes; obesity; malignancy; immunosuppression; and deprivation. Clinical prognostic scores have been developed, e.g. 4C score (https://isaric4c.net/risk/4c). Some patients suffer prolonged symptoms ('long COVID'). Longer-term health sequelae are unclear.

Prevention

Infection control precautions are essential to avoid hospital transmission:

- Wear gloves, aprons/gowns, masks; wash/alcohol gel hands regularly.
- Isolate or cohort cases; optimize ventilation; physically separate patients as far as possible (ideally >2m) to minimize transmission from occult cases.
- Follow local guidelines for aerosol-generating procedures.
- Vaccination ↓ risk of severe disease and may ↓ transmission. The emergence of several viral variants raises concern of vaccine escape.
- Community interventions focus on reducing interaction to minimize opportunities for transmission; and hand and respiratory hygiene +/− masks.

Management of pneumonia: children

Treatment

- Use local guidelines if available; WHO guidelines are given in Table 5.5. Parenteral antibiotics should be given for at least 5d in severe pneumonia.
- HIV+ve and/or severely malnourished children require broad-spectrum antibiotic coverage. Treatment for PCP with high-dose cotrimoxazole (and for CMV) should be considered for HIV+ve infants with severe pneumonia (➲ Special aspects of paediatric HIV/AIDS, p. 129).

Supportive care

- Oxygen—measure O_2 sats and provide O_2 (usually by concentrator) if O_2 sats <90% or marked respiratory distress. If concentrators are scarce, the supply can be split to two patients. Oxygen can also be delivered by continuous positive airway pressure (CPAP), esp. effective for newborns and infants.
- Analgesia if pleuritic pain.
- Ensure adequate fluids, but avoid overhydration.
- Prompt IV antibiotics in very young children, such as neonates, as they become unwell very rapidly.

Review treatment after 48h. In infants and children, pneumonia is usually a clinical diagnosis and CXR is reserved for those not improving with treatment at 24–48h or if other cause of respiratory distress is suspected, e.g. pneumothorax or foreign body. Clinical deterioration or failure to improve → CXR to check for lung abscess, empyema, cavities, or TB and change to second-line antibiotics or treat as indicated by the CXR.

Table 5.5 Empiric treatment of childhood pneumonia

Clinical picture	Parenteral	Oral (may follow IV in severe pneumonia)
Severe pneumonia first line	A. G	Ax
	Or Ct*	
Severe pneumonia second line if staphylococcal pneumonia is suspected	Clox + G	Clox
Pneumonia		Ax

*Ct is an alternative, but it is best to reserve Ct for treatment failures.

Key to antimicrobials dosing for children (>1mth):

A Ampicillin 50mg/kg IM or IV qds.

Ax Amoxicillin 40mg/kg per oral dose bd.

Clox Cloxacillin 50mg/kg qds IV/IM, 25mg/kg qds oral.

Ct Ceftriaxone 80mg/kg IM/IV od.

G Gentamicin 7.5mg IM or IV od.

Data from World Health Organization, *Pocket Book of Hospital Care for Children*, 2013.

Further reading

British Paediatric Formulary available online (free to many low-resource countries through HINARI and UK users): Available at: http://www.bnf.org/bnf/index.htm

WHO guidelines available at: https://www.who.int/maternal_child_adolescent/documents/9241546700/en/

Paediatric acute respiratory infections: epiglottitis

Epiglottitis is an acute bacterial infection of the epiglottis and arytenoids, the surrounding tissue, and cartilages, mainly affecting children aged 2–7yrs and mainly caused by Hib.

Direct or haematogenous infection of the upper airway → rapid swelling and risk of airway obstruction. Hib conjugate vaccine substantially ↓ incidence. Severe disease occurs where immunization coverage is low. In older individuals, *Streptococcus pneumoniae*, *Haemophilus parainfluenzae*, group A streptococci, and *Staphylococcus aureus* can cause a similar illness.

Clinical features

Typically starts suddenly and progresses rapidly. The affected child presents with sudden onset of high fever, sore throat, and muffled voice → stridor, respiratory distress, and drooling of saliva. The child appears toxic, refuses to eat or drink, and prefers to sit upright, leaning forward in an effort to maintain patency of the airway; may have loss of voice (aphonia) and dysphagia.

Diagnosis

Consider epiglottitis in any young child with compatible clinical presentation, esp. if not immunized against Hib. Intubation is dangerous and should be undertaken only if expert. Visualization of a large, swollen, cherry-red epiglottis by laryngoscopy at the time of intubation confirms the diagnosis. See Box 5.2 for differential diagnosis of acute upper airways obstruction.

Management

Epiglottitis is a medical emergency. Aim to prevent airway obstruction and eradicate the infection. Before a definitive airway is established, make all attempts to minimize distress to the child, as agitation will compromise the airway.

- Give humidified O_2.
- Make urgent arrangements for inserting an artificial airway (preferably nasotracheal) even if there is no current respiratory distress.
- Be prepared to perform a tracheostomy if endotracheal intubation fails.
- Until the airway has been inserted *do not*:
  - Examine the throat (reflex laryngeal spasm may cause complete airway obstruction).
  - Attempt venepuncture (anxiety and pain may → acute laryngeal spasm).
  - Send the child for CXR (immediate intervention will be necessary if airway obstruction occurs).
- Once definitive airway inserted take samples for FBC and cultures of blood and a swab of the epiglottis.
- Give antibiotics when the airway is safe: IV ceftriaxone.

Note: adrenaline and corticosteroids are ***not*** effective in epiglottitis. Once the airway is inserted, most children improve rapidly. The epiglottitis resolves after a few days of antibiotics, and the patient can be weaned from the endotracheal tube or NGT.

Box 5.2 Differential diagnosis of acute upper airways obstruction in children

- Croup (most common).
- Bacterial tracheitis.
- Epiglottitis.
- Diphtheria.
- Severe tonsillitis.
- Infectious mononucleosis.
- Laryngeal foreign body.
- Smoke or steam inhalation.
- Trauma.
- Laryngomalacia.

Acute laryngotracheobronchitis: croup

Laryngotracheobronchitis (LTB; croup) is the commonest form of upper airway obstruction in childhood, usually occurring between 3mths–5yrs of age. LTB initially affects the mucosa of the nose and nasopharynx, → larynx and bronchial tree. In young children inflammation → submucosal oedema and narrowing of the airway. Human parainfluenza viruses cause ~75% cases; other causes include adenoviruses, RSV, influenza, and measles.

Clinical features

LTB begins as a mild URTI with mild barking cough, low-grade fever, and intermittent stridor. Over the ensuing few days, progressive compromise of the airway → ↑ coughing, stridor becomes continuous (+/– wheeze), and signs of respiratory distress develop, including nasal flaring, suprasternal, intercostal, and subcostal recession (lower chest wall in drawing), associated with a prolonged, laboured expiratory phase of respiration. Symptoms are characteristically worse at night. Crying and agitation ↑ symptoms and the child prefers to sit up in bed or be held upright. Examination reveals reduced breath sounds, wheezes, and crackles. Most children improve spontaneously within 48–72h, but some → severe airway compromise and require further intervention to avert respiratory failure.

A 2° bacterial infection or tracheitis can occur due to *Staphylococcus aureus*.

Diagnosis of LTB is clinical.

Management

Indications for admission are listed in Box 5.3.

- Give dexamethasone 150 micrograms/kg IV/IM/oral, or prednisolone 1–2mg/kg oral, or nebulized budesonide 2mg stat; repeat at 12h if necessary.
- Give humidified O_2.
- Give IV fluids if moderate to severe respiratory distress.
- Ensure minimal disturbance as ↑ symptoms on agitation.
- Observe closely for signs of ↑ airway obstruction.
- If severe airway obstruction develops (cyanosis, air hunger, restlessness) give nebulized adrenaline (give 400 micrograms/kg up to max. 5mg, of 1 in 1000 (1mg/mL) solution, repeated after 30min if required), +/– tracheostomy or nasotracheal intubation.

Note

- Sedation is contraindicated in croup because it masks restlessness, which is a major indicator of the severity of airway obstruction and the need for tracheostomy or nasotracheal intubation.
- Expectorants, bronchodilators, and antihistamines are not helpful in croup.

Box 5.3 Indications for admission in a child with croup

- ↑ stridor or respiratory distress.
- Severe stridor at rest.
- Hypoxia or cyanosis.
- Restlessness, lethargy, or unconsciousness.

Managing milder episodes at home

- Children with mild croup can be managed at home, but must be watched closely for signs of worsening respiratory obstruction.
- Management is supportive.

Bacterial tracheitis

Presentation similar to croup, but patient is systemically more unwell. It may affect any age group and does not respond to croup treatment. Unlike epiglottitis, bacterial tracheitis rarely → airway obstruction. Causes include *Staphylococcus aureus*, group A streptococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella* spp., other Gram –ves, and anaerobes. There is diffuse inflammation of the larynx, trachea, and bronchi with formation of an adherent or semi-adherent mucopurulent membrane in the trachea.

Clinical features

Include:

- Fever.
- Bark-like/brassy cough.
- Hoarseness.
- Respiratory distress.
- Sepsis.

Other differential diagnoses include:

- Diphtheria.
- Epiglottitis.
- Peri-tonsillar or retropharyngeal abscess.

Diagnosis

This is clinical, supported by ↑ WBC; CXR may show narrowing of trachea. Direct visualization and positive blood culture, or culture of purulent tracheal secretions by laryngo-tracheobronchoscopy, provides definitive diagnosis.

Treatment

Involves airway management and administration of broad-spectrum antibiotics. Affected children may decompensate acutely → ↑ respiratory distress and sepsis.

Bronchiolitis

Bronchiolitis is common among children aged <2yrs (peak 3–6mths). In >50% of cases it is caused by RSV. Other causes incl. human metapneumovirus, adenovirus, and parainfluenza virus. Source of infection is usually an older child or adult with a minor respiratory illness. Risk factors for severe bronchiolitis incl. low birth weight, age <6wks, and comorbidity such as lung disease, congenital heart disease, and immune deficiency.

Clinical features

Characteristically begins as a URTI; the infant appears slightly unwell, with low-grade fever, a blocked nose, serous nasal discharge, cough, and feeding difficulty. Within 24–48h, the signs of airway obstruction appear with paroxysmal wheezy cough, dyspnoea, and irritability. Breast- and bottle-feeding become difficult as ↑ RR does not give enough time for sucking and swallowing. Clinical features tend to be most severe days 4–6 of illness. Examination reveals tachypnoea, nasal flaring, and intercostal subcostal recession. Chest is hyper-resonant with obliteration of the cardiac dullness due to hyperinflation. Wheeze and fine crackles are heard on auscultation. The liver and spleen may be palpable due to hyperinflation.

Diagnosis

Bronchiolitis is a clinical diagnosis. CXR may show hyperinflation (flattening of the diaphragm) +/– ↑ perihilar infiltrates.

Management

Markers of severity requiring admission:

- Apnoea.
- Hypoxia (O_2 sats <92%).
- Reduced feeding.
- RR >70 breaths/min.
- Moderate or severe recessions.
- Nasal flaring.
- Grunting.

Even if markers of severity are absent, consider admission if risk factors, or if early in the course of illness; most of infants are asymptomatic by 2wks.

- Give humidified O_2 via a nasal catheter.
- CPAP if more severe and available. Need for intubation is very rare.
- Ensure adequate fluid intake, feed via NGT or give IV fluids for severe respiratory distress.

Note

- Antibiotics are indicated if any associated pneumonia.
- Corticosteroids are of no benefit.

Whooping cough

Bordetella pertussis commonly affects infants and young children, with the highest mortality <3mths. Mild infections in adolescence and adults are likely underdiagnosed and are the source of infection for infants. *B. parapertussis* causes a similar illness to *B. pertussis*.

Clinical features

Incubation is 6–20d.

- Initially URTI symptoms which last 1–2wks. Fever not usually high.
- Paroxysms of severe coughing with a 'whoop' are classical features. The 'whoop' is caused by forced inspiration against a partly-closed glottis and can → cyanosis and hypoxic syncope.
- Child commonly drools and vomits after coughing, and may become exhausted.
- Wheezing does not occur.
- After 1–3wks of whooping, a more tolerable chronic cough may persist for several weeks; adults and older children may have a chronic cough throughout.
- Infants <6mths do not whoop, but may become apnoeic and have non-specific signs of respiratory distress (difficult to differentiate from bronchiolitis (Bronchiolitis, p. 197) caused by respiratory viruses).
- Many cases, esp. older children are uncomplicated and self-limiting; however, illness can persist for weeks to months and → bronchiectasis and malnutrition.
- Prolonged coughing may → petechiae on face/upper body, conjunctival haemorrhages, and rectal prolapse.
- Death is unusual in older age groups, may be due to 2° pneumonia, or encephalopathy (↓ consciousness not due to hypoxia, seizures, or brain damage).

Diagnosis

Normally made clinically. The WCC in infants usually shows a lymphocytosis, which is less common in older patients. Culture is difficult—a per-nasal swab or a nasopharyngeal aspirate sample can be taken (PCR if available).

Management Essentially supportive. Erythromycin is recommended, and ↓ transmission, but has little effect in modifying whooping cough. Antihistamines, pertussis immunoglobulin, salbutamol, and steroids are all ineffective.

Prevention Routine immunization.

Lymphocytic interstitial pneumonitis

LIP was a common cause of chronic pulmonary disease in children with HIV, but is uncommon in those being treated with ART. It is uncommon in adults. LIP also occasionally occurs in patients with EBV, human T lymphotropic virus (HTLV), lymphoproliferative disorders, and autoimmune disease. Pathologically, there is a pleomorphic lung infiltrate of activated lymphocytes, plasma cells and immunoblasts.

Clinical features

May be asymptomatic in the early stages. Symptoms usually progressive:

- Chronic cough.
- Dyspnoea.
- Parotid enlargement.
- Generalized lymphadenopathy.
- Hepatosplenomegaly.
- Digital clubbing.
- Wheezing.

+/– other features of underlying HIV.

Diagnosis

This is suggested by the characteristic clinical features.

- CXR findings include bibasal interstitial or small nodular infiltrates which coalesce → alveolar consolidation; widened mediastinum; and perihilar adenopathy.
- Serum LDH is often ↑ to 300–500IU/L.
- Look for underlying immunosuppressive disease, especially HIV.

Differential diagnoses include varicella pneumonia, miliary TB, and metastatic carcinoma. Definitive diagnosis requires open lung biopsy, which is rarely performed in view of its complications.

Treatment

Asymptomatic children require no treatment, but follow up for clinical and/or radiological signs of deterioration. For symptomatic children:

- O_2.
- Prednisolone 2mg/kg oral daily; treat for 4wks then gradually ↓ dose.
- Long-term steroid therapy may be required if symptoms recur.
- Bronchodilators may be used to treat children with wheeze.
- Treat the underlying cause: ART for HIV+ve patients.

Diphtheria

Corynebacterium diphtheriae causes infection of the nasopharynx and occasionally skin and mucous membranes. Its endotoxin potentially → fatal effects on the heart, kidney, and peripheral nerves. Death occurs in >50% without treatment, and in 5–10% despite treatment. Children <5yrs and adults >40yrs have a worse prognosis. Although incidence is ↓ worldwide, it remains a significant problem in some developing countries without effective immunization programmes.

Transmission

This is by droplets or secretions from infected patients. Incubation is 2–5d. Patients are infectious for >1mth; however, some become carriers.

Clinical features

Incubation is >2–5d (7d cutaneous diphtheria).

There may be non-specific symptoms:

- Fever.
- Chills.
- Malaise.
- Nausea.
- Vomiting.
- Headache.

Local

Mucosae are initially red and oedematous → necrosis of epithelium. An inflammatory grey-white pseudo-membrane forms at the site of infection (commonly the tonsils and oropharynx); it is adherent and separates with bleeding. There is sore throat (may → dysphagia), cervical lymphadenopathy, and halitosis (Box 5.4). Neck is often swollen with oedema and enlarged lymph nodes—the 'bull neck' appearance. Palatal paralysis by toxin produces a nasal quality to the speech.

Tracheo-laryngeal

- Hoarseness.
- Dry cough.
- Rarely, airway obstruction.

Cutaneous

Pustules and ulcers with a grey membrane (rare).

Systemic effects of toxin

- Myocarditis (10%).
- Heart block (often >1wk after acute infection; can → death up to 8wks after initial illness).
- Murmurs.
- Heart failure.
- Demyelination → peripheral neuritis (often ~6wks after initial illness).
- Paralysis of soft palate, ocular, and intercostals muscles.
- There may be renal failure (tubular necrosis) and pneumonia.

Malignant diphtheria Indicates rapid spread of membranes, neck oedema, adenitis, stridor, and shock.

Diagnosis

Treat on suspicion—do not wait for confirmation. Culture throat swabs of membrane, ECG (look for ectopics, ST and T wave changes, right bundle branch block (RBBB), complete heart block), U&Es, and FBC.

Treatment

Give antitoxin urgently. A test dose of diluted diphtheria antitoxin should first be given intradermally to exclude hypersensitivity; then give 10,000–40,000 units by IV infusion for mild–moderate disease, and 40,000–100,000 by IV infusion for severe disease. Antitoxin is made from horse serum, so beware of anaphylaxis which is rare, but potentially fatal. Have adrenaline drawn up. Tracheostomy may be lifesaving; do not delay if there are signs of respiratory distress. Give high-dose antibiotics IV (penicillin, erythromycin, cephalosporin, and tetracycline are all effective).

Prevention Routine childhood immunization prevents disease. Recovering patients should also receive a booster dose of diphtheria vaccine, as well as close contacts.

Box 5.4 Causes of sore throat and tonsillar exudates

- *Streptococcus pyogenes* (sequelae are rheumatic heart disease and glomerulonephritis).
- Mild viral infections (less common to have exudates).
- *Corynebacterium diphtheriae*.
- EBV: infectious mononucleosis.
- *Neisseria gonorrhoeae*.
- 2° syphilis.
- Herpes simplex virus—especially if HIV+ve.
- Lassa virus.
- *Fusobacterium necrophorum* (as part of Lemierre's syndrome).

Pleural effusion

Pleural effusion is the presence of fluid in the pleural cavity, commonly unilateral. See Box 5.5 for causes.

- Exudates are inflammatory fluid collections caused by an underlying infective/inflammatory disease. They are generally straw coloured, unilateral, cellular pleocytosis is common, and fluid LDH levels are generally high. Protein is >50% of serum protein or >30g/L.
- Transudates: low protein content, are generally bilateral, and cellular pleocytosis is minimal. All oedema-causing conditions—congestive cardiac failure (CCF), nephrotic syndrome, liver failure, anaemia, and hypoalbuminaemia may → transudative pleural effusions.
- Chylothorax: milky fluid with a high lipid content, caused by leakage from the thoracic duct due to damage by filariasis or a tumour.
- Empyema: is infected effusion. Cells are neutrophils, and in some cases, frank pus; pH <7.2 (Box 5.6).
- Haemothorax: pure blood or heavily bloodstained fluid.

Box 5.5 Causes of pleural effusion

Exudates

- TB.
- Lung cancer.
- Pneumonia.
- Mesothelioma.
- Autoimmune diseases (e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)).
- Sub-diaphragmatic infections/abscesses.
- Metastatic carcinoma.
- PE.
- Pancreatitis.

Haemothorax

- Trauma.
- Mesothelioma.
- Metastatic carcinoma.
- Vascular pleural adhesions.

Transudates

- LVF.
- Liver disease especially with ascites.
- Nephrotic syndrome.
- Anaemia and hypoproteinaemia.
- Pericardial disease.

Chylothorax

- Filariasis.
- Lymphoma.
- Trauma to the thoracic duct.
- Metastatic carcinoma.

Clinical features of pleural effusion

Pleuritic pain may be present if acute—less common in TB (chronic inflammation). Patients may be tachypnoeic and dyspnoeic. Chest wall expansion is ↓ on affected side and there is stony dullness to percussion with ↓ tactile fremitus and vocal resonance and ↓ or absent breath sounds. Signs are commonly detected at the bases posteriorly, and in the mid-axillary line.

Box 5.6 Empyema

- Pus in the pleural space.
- A complication of a bacterial pneumonia, aspiration pneumonia, or rupture of a liver or lung abscess and less commonly TB.
- Suspect in any patient with persistent (often high spiking) fever, with pleuritic pain and pleural effusion.
- Diagnosis by aspiration of pleural fluid for Gram stain and culture.
- Putrid odour indicates anaerobic bacterial infection.
- High protein, high cell count, pH <7.1 or high LDH level (>60% of serum LDH or >1000) suggests an empyema is developing, and needs to be drained.
- Give broad-spectrum antibiotics (co-amoxiclav; or ceftriaxone; cefotaxime plus metronidazole). Cultures are often –ve in which case empirical therapy must continue.
- Intercostal tube drainage to dryness (<20mL fluid in 24h) and 6wks of antibiotics will cure most cases.
- Decortication may be required if a prolonged course of IV antibiotics combined with repeated US-guided aspiration fails.
- Recurrent empyema presents a particular problem if HIV+ve. Culture often shows mixed growth, response to therapy poor, and surgical risk too high for decortication. In these cases, prolonged antibiotics and a fistula or short drain into an ileostomy bag can be helpful.

Diagnosis

The presence of fluid is confirmed by CXR or USS. Aspiration of 50–100mL is generally done for diagnosis, but in patients with respiratory distress 700–1000mL is aspirated to relieve symptoms. Fluid is best withdrawn posteriorly with the patient leaning forward and the needle inserted above the rib one or two intercostal spaces below the upper level of dullness. Fluid should be sent for protein, pH, cytology, Gram and AFB staining, and LDH levels and appropriate cultures (Box 5.7). If no cytology available, ADA can be used as a marker of lymphocytes and macrophages in pleural fluid.

Management Treat cause of effusion. Where fluid → dyspnoea, repeated aspirations or chest tube insertion may be beneficial. Where recurrence is a problem, pleurodesis may be performed.

Box 5.7 Diagnostic features of pleural effusions

- *Exudates*: protein >30g/L (+ normal serum proteins) or fluid protein >50% of serum protein, LDH >200IU, fluid:serum LDH ratio >0.6.
- *Transudates*: protein <30g/L, LDH <200, LDH ratio <0.6.
- *Neutrophilia*: bacterial pneumonias, empyemas.
- *Lymphocytosis*: TB, lymphomas, viral infections.
- *Abnormal cytology*: carcinomas, mesotheliomas.
- *Low pleural fluid glucose*: RA, infections, malignancies.
- pH <7.2 suggests empyema developing, consider tube drainage.
- Positive Gram stain confirms empyema.

Lung abscess

A suppurative cavitating infection of the lung parenchyma, commonly caused by aspiration of mouth anaerobes, less often by blood-borne infection. Melioidosis is a particularly severe cause of lung abscess in Southeast Asia, Indian subcontinent, and North Australia (see Box 5.8 for causes).

Clinical features

Patients present with cough, fever, chills, chest pain, and haemoptysis. Gingivitis with poor dentition, the usual source of the bacteria, is often present. When the abscess communicates with a bronchus, copious quantities of purulent sputum, often blood streaked, are expectorated. Clubbing develops rapidly. If lung abscess ruptures into pleural space → empyema. Chronic abscesses with waxing and waning symptoms may result from inadequate antibiotic therapy.

Diagnosis

Characteristically the CXR shows a rounded opacity with an air–fluid level. Multiple abscesses suggest a blood-borne infection, e.g. infected pulmonary emboli or tricuspid endocarditis. Leukocytosis with ↑ ESR and CRP are typical. Foul-smelling sputum indicates anaerobic infection. If abscess does not resolve with antibiotics, bronchoscopy may be performed to seek an endobronchial obstruction (foreign body, malignancy, bronchial adenoma).

Management

Give IV antibiotics until fever, ESR, CRP, and leukocytosis settle—may take weeks. Co-amoxiclav, ceftriaxone, or cefuroxime are good initial choices plus metronidazole and may be modified according to cultures. Consider an anti-staphylococcal antibiotic (e.g. flucloxacillin or clindamycin) in influenza outbreaks or when cultures indicate.

Box 5.8 Causes of lung abscesses

Pulmonary aspiration

Most occur in the right lung; aspiration while supine results in abscesses in apical segment of the lower lobe or posterior segment of the upper lobe. Often caused by anaerobes of gingival origin.

Bronchial obstruction

Due to lung CA or inhaled foreign body. Caused by mixed anaerobes.

Bacteraemia/septicaemia

Often multiple abscesses from sites such as right-sided endocarditis, infected IV cannulae, IV drug abuse. Common causes are *Staphylococcus aureus* and *Streptococcus mill*eri.

Primary infection with cavitation

TB or as a complication of severe pneumonia with *S. aureus*, *Klebsiella pneumonia*, or *Nocardia asteroide*s (esp. in immunosuppression).

Spread from subphrenic or hepatic abscess

Produces 2° abscess, often in the right lower lobe. Due to *Entamoeba histolytica*, coliforms, *Streptococcus faecalis*.

Cavitating lesions seen on CXR, mimicking abscesses

May be caused by:

- TB.
- Paragonimiasis.
- Fungal infection.
- Cavitating squamous cell CA.
- Pulmonary infarction.
- Granulomatosis with polyangiitis.

Fungal pulmonary infections

Fungal spores are found airborne and in soil and are often abundant in bird and bat faeces. Human–human transmission does not appear to be a problem. The infections depend on the immune status of the individual and the level of exposure. Many cases are asymptomatic, and illness may present as:

- Self-resolving pneumonitis (acute pulmonary form): cough, chest pain, fever, joint pains, malaise, occasionally erythema nodosum or erythema multiforme. Specific therapy may be required in more severe cases.
- Localized cavitation, nodules, or calcification may be asymptomatic and found on CXR taken for other reasons. No treatment is required. However, since they can resemble lung tumours, they may be diagnosed only at surgery.
- Persisting or spreading cavitation → chest pain, cough, and sometimes haemoptysis (which can be heavy). Surgery and antifungal therapy may be required. Resembles pulmonary TB.
- Acute or chronic systemic spread. Patients present with fever, often marked ↓ weight, skin lesions. If acute, there may be signs of lung disease and purpura due to thrombocytopenia and hepatosplenomegaly. Disseminated disease is fatal in the absence of systemic antifungal therapy.

Severe fungal pneumonia is rare. People with diabetes, the elderly, pregnant women, and children (especially neonates) are predisposed to spreading and cavitation. Immunosuppression or neoplasia predispose to acute disseminated disease. See Box 5.9 for management of systemic fungal infections.

Aspergillosis

Aspergillus is ubiquitous and clinical infection is rare. Most infections are caused by *A. fumigatus*, *A. flavus*, or *A. niger* in predisposed hosts, especially patients with asthma or post-TB cavitation.

Clinical forms and management

- *Allergic bronchopulmonary aspergillosis*: persistent endobronchial infection → severe asthma and, with time, a chronic cough (producing mucoid plugs) and dyspnoea. CXR may show shadowing in the peripheral fields. Eosinophilia is a feature. Manage with steroids and itraconazole if possible. May → proximal bronchiectasis.
- *Aspergilloma*: a fungal ball that often develops in a pre-existing cavity (commonly due to TB). Aspergillomas are extremely variable in their course, ranging from undergoing spontaneous lysis to fatal haemoptysis. Intermittent cough is often the only sign, but haemoptysis may develop. CT scan appearances are distinctive, showing a mass attached to the interior of the cavity, and overlying pleura usually thickened. If necessary, the aspergilloma should be surgically excised; prolonged courses of itraconazole have produced improvement in some patients.
- *Invasive aspergillosis*: occurs in brain; kidney, liver, and skin of the severely immunocompromised (e.g. bone marrow transplant recipients). Attempt to ↓ immunosuppression, if possible. Amphotericin B (0.5–1.0mg/kg IV od, to a total dose of 2–2.5g) has been standard therapy (it is a toxic drug), but for confirmed invasive aspergillosis voriconazole may be more effective.

Diagnosis of Aspergillus infection

This is often difficult.

- Microscopy of skin lesion scrapings, sputum, or pus.
- Serology (*Aspergillus* precipitins), fungal cultures.
- Skin prick tests to *Aspergillus* and *Aspergillus* RAST test are useful in allergic bronchopulmonary aspergillosis.
- In invasive aspergillosis, the CXR or CT appearances may give a clue, being typically more severe than expected from clinical examination.
- Isolated chronic lung lesions (mycetomas) may only be distinguished from lung tumours at surgery.
- Galactomannan levels (cell wall component of *Aspergillus*) are used in high-resource settings, but require careful interpretation.

Histoplasmosis

This occurs in two forms, and commonly → disseminated disease in HIV-infected patients:

- Small-form histoplasmosis (caused by *Histoplasma capsulatum* var. *capsulatum*): occurs in the Americas, Asia, and eastern Africa. This → acute or chronic pulmonary infections, pericarditis, or progressive disseminated histoplasmosis in immunocompromised individuals. Disseminated small-form histoplasmosis affects bone marrow, spleen, liver, lymph nodes, and skin (papules, ulcers). A chronic form in immunocompetent patients → persistent painful oral ulceration and/or hypoadrenalism. Complications include laryngeal ulceration, endocarditis, and meningitis.
- Large-form or African histoplasmosis: (*H. capsulatum* var. *duboisii*.) occurs in central and west Africa. African histoplasmosis is either a focal disease affecting bone, skin, and lymph nodes or a progressive disseminated disease affecting mucosal surfaces, esp. the GI tract and lungs.

Blastomycosis

A systemic infection caused by *Blastomyces dermatitidis* that occurs in northern America, Africa, India, and Middle East. It causes chronic pulmonary or disseminated disease (involving both lung and skin). Skin lesions are commonly an initial single nodule, then → crusted plaques, ulcers, and abscesses. Complications include lytic bone lesions (esp. axial skeleton), and GI tract disease (esp. epididymitis).

Coccidioidomycosis

A disease of semi-arid regions of the Americas caused by the fungus *Coccidioides immitis*. It is inhaled into alveoli, where it rounds up and divides to form a large spherule with a thick outer wall. The clinical features are typically varied with dissemination → meninges, joints, and skin. It commonly disseminates in patients with advanced HIV.

Paracoccidioidomycosis

A granulomatous disease caused by the fungus *Paracoccidioides brasiliensis*. It occurs sporadically in south and central America where it is the most common systemic mycosis. An acute form of the disease occurs in children and adults <30yrs, while a chronic form is more common in 30–50yr-olds, especially agricultural workers living in endemic areas. The male:female ratio is >10:1.

Acute form

Presents with generalized lymphadenopathy, moderate hepatosplenomegaly, fever, and ↓ weight over several months. The nodes may become fluctuant. Involvement of mesenteric and hepatic perihilar nodes → an appendicitis-like picture or obstructive jaundice. Complications include lytic bone lesions, small bowel disease, multiple mucocutaneous lesions (lymphatic/haematogenous spread). Pulmonary involvement is uncommon. Immunosuppression can → severe superinfection (e.g. TB, *Cryptococcus*, pneumonia).

Chronic disease

Normally presents with lung disease—dyspnoea, cough (rarely haemoptysis and fever), with extensive involvement on CXR. Mucocutaneous lesions are common on skin (face, limbs); painful lesions in the mouth, pharynx, or oesophagus inhibit eating, → marked ↓ weight. Other features—ulcerated tongue, hypoadrenalism. Chronic inflammation and fibrosis may → tracheal/laryngeal fibrosis, pulmonary fibrosis, and bowel obstruction due to enlarged lymph nodes.

Box 5.9 Management of systemic fungal infections

- Follow local guidelines.
- Amphotericin B (↑ daily dose (after test dose) from 0.25mg/kg/d IV to 1.0mg/kg/d, if renal function permits) to a cumulative total of >15mg/kg.
- (Alternative: fluconazole 200–400mg oral od for 6–18mths depending on specific fungus.)
- Meningitis due to coccidioidomycosis requires fluconazole 400–800mg oral od for 9–12mths.
- Patients with histoplasmosis may be switched to oral itraconazole (200mg oral tds for 3d, then 200mg oral bd for total treatment duration of 12wks) after improvement on amphotericin B.
- Surgery may be required for management of chronic sequelae in paracoccidioidomycosis.

Paragonimiasis (lung fluke)

A persistent lung disease, occurring widely around the globe, but especially in East Asia, which is caused by >15 different species of *Paragonimus* trematodes; ~22 million people are infected worldwide (Fig. 5.1).

Transmission

Humans are infected by eating undercooked freshwater crabs and crayfish infected with the metacercariae. The immature flukes burrow out of the human intestine into the peritoneum, where they mature and tunnel their way into the lungs (Fig. 5.1). Here, they cause inflammation, haemorrhage, and necrosis of the lung parenchyma. Adult flukes (stout, bean-shaped, ~1cm long) live in cavities in proximity to airways. Ova are expelled either in expectorated sputum or in the faeces after being swallowed. Flukes that miss the lungs produce extrapulmonary symptoms (due to cysts, granulomas, and abscesses) in muscles, abdominal viscera, brain, and genitalia.

Clinical features of paragonimiasis

Days or weeks after eating infected food, migration of the flukes within the peritoneum and pleura → fever, rashes, urticaria, abdominal, and chest pain, wheeze, cough, or discomfort.

The classic feature of chronic pulmonary disease is a persistent cough with production of thick brownish-red sputum (due to the presence of ova and flukes). The CXR resembles TB, except that cavities are often basal. CXR changes may also include areas of consolidation, and pleural effusions. Physical examination of the chest often reveals little and the patients appear quite well (unlike TB).

Aberrant migration of the flukes may produce signs of a cerebral SOL (epilepsy, ↑ ICP, psychiatric syndromes, meningeal irritation) or spinal SOL, necrosis of abdominal viscera, transitory subcutaneous swellings. Extrapulmonary disease may occur in the absence of pulmonary signs, but this is uncommon.

Diagnosis

Presence of characteristic ova in the sputum, faeces, or effusion; serology.

Management

Praziquantel 25mg/kg oral tds for 2–3d → rapid symptomatic improvement, although radiological changes may take months to improve. Treatment of cerebral infection may → neurological deterioration, in some cases → seizures and coma. Beware of ↑ ICP due to dying parasites. Treat cautiously and consider dexamethasone 4mg IV qds as cover.

Prevention Improve health education to ↓ consumption of undercooked crustaceans; mass treatment of persons in endemic areas.

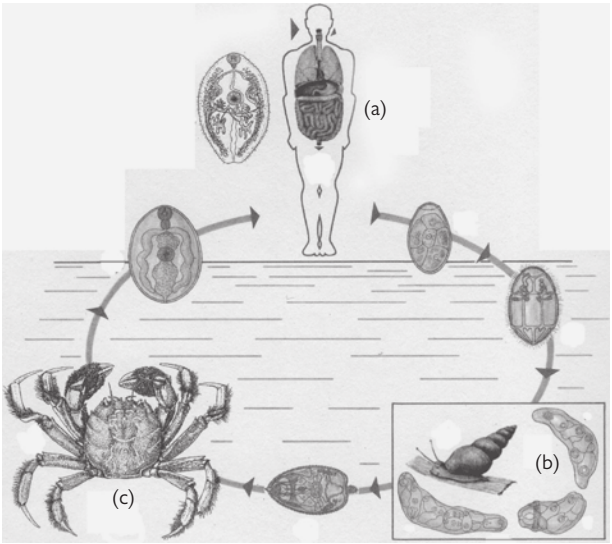


Fig. 5.1 Life cycle of *Paragonimus* lung flukes. (a) Humans are the definitive host, along with a range of domestic canines and felines. The adult fluke lives in cavities in the lung; ova are either coughed or defecated into fresh water. Miracidia emerge, and infect aquatic snails (b), in which development into cercaria takes place. These encyst as metacercariae on the muscles of freshwater crabs and crayfish (c), which are eaten uncooked. The metacercariae contain immature flukes which bore through the intestinal wall, migrate through the diaphragm into the lungs. The mature flukes are hermaphrodite, and without mating produce ova 2–3mths after infection, completing the life cycle. Adapted from Piekarski, G, Medical Parasitology in Plates, 1962, with kind permission of Bayer Pharmaceuticals.

Tropical pulmonary eosinophilia

TPE occurs in <1% of filarial infections, and occurs in areas where lymphatic filariasis is endemic. *Wuchereria bancrofti* and *Brugia malayi* mature within lymphatics. Female worms discharge millions of microfilariae, which are trapped and destroyed within the lungs in some individuals → acute or chronic eosinophilic alveolitis.

Clinical features

Young adults are generally affected. Nocturnal cough associated with wheezing may occur, due to the nocturnal periodicity of microfilaraemia. Low-grade fever, malaise, and ↓ weight may occur. Wheezes and crackles are heard in severe or advanced cases, but in many patients respiratory examination is normal. Significant eosinophilia is typical, with total eosinophil counts >3000/mm3; IgE levels are elevated. Symptoms do not correlate with the degree of eosinophilia. Microfilaraemia is rarely observed in TPE. Filarial serology is +ve, but may be unhelpful in endemic areas. CXRs may be normal or show a reticulonodular appearance. In long-standing cases, features of pulmonary fibrosis are seen. Pulmonary function tests (PFTs) show a mixed restrictive and obstructive pattern with diffusion abnormalities prominent in long-standing cases.

Management

Diethylcarbamazine (DEC) 5mg/kg daily in three divided doses × 3wks → rapid improvement in most patients. Those who respond poorly should have a second course of DEC for a longer duration. ~20% of patients relapse, requiring repeated courses of DEC. Doxycycline kills the endosymbiont bacteria *Wolbachia* in filarial worms, but this is not of proven efficacy in TPE.

Asthma

Asthma is a syndrome of reversible bronchial obstruction → episodic wheezing and shortness of breath (SOB). There is genetic susceptibility, and triggers include:

- Protein allergens, e.g. dust, food, pets in atopic individuals.
- Low-molecular-weight allergens, e.g. isocyanate in industry.
- Infections, especially viral in children (Box 5.10), e.g. RSV.
- Environmental or occupational pollutants, e.g. smoke, automobile exhausts, and industrial dusts → irritation and can ↑ existing asthma.

Epidemiology of asthma

~10% of young adults in resource-poor countries are atopic, with ↑ prevalence in Ghana and similar areas. This is likely multifactorial and theories include the immunological effect of ↓ parasite exposure, altered diet, and obesity and ↑ house dust allergen exposure.

Pathology

Constant exposure to environmental triggers → constant mucosal inflammation. Acute symptoms may be caused by exposure to any exacerbating factor and may ↑ by beta-blocker therapy, aspirin, or non-steroidal anti-inflammatory drugs (NSAIDs); exercise commonly → wheezing.

Diurnal variation is common, due to the circadian variation in endogenous cortisol. Symptoms are generally worse on waking and in severe cases may → nocturnal awakening with cough, chest tightness, and dyspnoea.

Exacerbating factors (e.g. cold dry air, pollen, fumes) → bronchial hyperresponsiveness, inflammatory bronchial wall oedema, and intra-luminal mucus accumulation → airway narrowing, airflow obstruction and distal air trapping.

Acute severe asthma either occurs for no reason or with infection or exposure to allergen/irritant.

Clinical features

- Breathlessness.
- Cough.
- Expiratory wheezing: best heard towards full expiration.
- Chest tightness.

Diagnosis of asthma

- Based on characteristic clinical features and history.
- Measurement of variability in peak expiratory flow rate (PEFR) is useful.
- Typical spirometry shows ↓ PEFR with >15% reduction in response to stimulus challenge, e.g. 6–10min of strenuous exercise. PEFR is <60% predicted or varies by >30%; or PEFR improves by >20% with bronchodilators or steroids.

Management

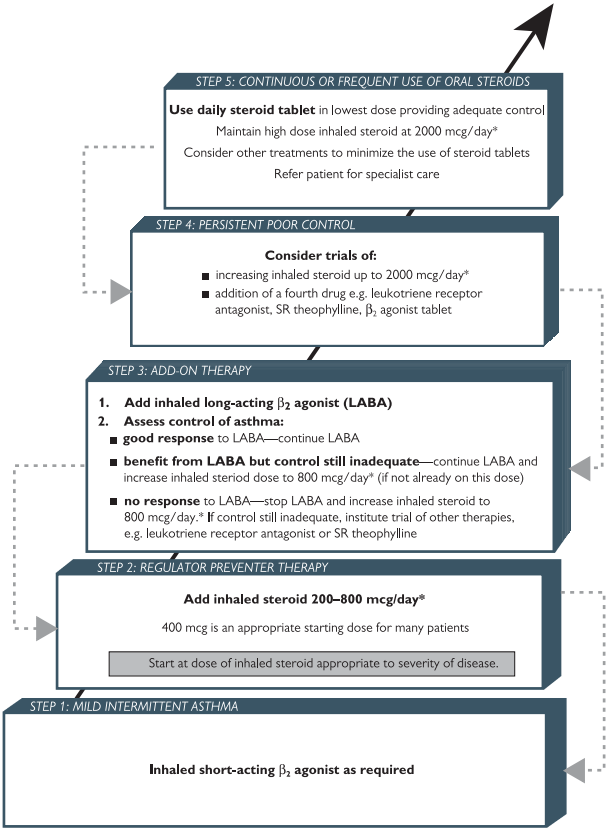
- Identify and avoid triggers (limited evidence of efficacy).
- Relieve acute symptoms with beta-agonist inhalers.
- Suppress chronic inflammatory airways hyper-reactivity with inhaled or oral steroids (good efficacy) or leukotriene antagonists (very expensive) (Fig. 5.2).
- Once asthma is controlled, therapy should be stepped down. Regular review is important. Patients should be maintained on the lowest dose of inhaled steroid.

Aims of treatment

- Freedom from symptoms, especially nocturnal asthma.
- Lung function in the normal range varying by <20% during 24h.
- Normal quality of life with self-management of condition.

Box 5.10 Paediatric note

- Ask about eczema and hay fever (in child and in family) as these suggest atopy, and are associated with asthma.
- In children <2yrs, a formal diagnosis of asthma is not usually given. Children <2yrs who wheeze and may need treatment (often caused by a viral trigger), may or may not later develop asthma and these episodes are termed 'viral-induced wheeze'.
- Management of asthma in children is based on age and response to treatment. In those aged 2–5yrs, start with occasional relief bronchodilators, then add regular preventer therapy if needed. This may be an inhaled steroid (or a leukotriene receptor antagonist if inhaled steroid cannot be used). A step-up from this would be to use both of these agents. If control is not achieved, specialist advice should be sought if possible.



* BDP or equivalent

Fig. 5.2 Summary of stepwise management in adults. BDP, beclometasone dipropionate; LABA, long-acting beta agonist. Reproduced with permission from the British Thoracic Society, BMJ Group. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/

Acute severe asthma

Ascertain the recent best or predicted PEFR, the current medication, esp. that recently taken for relief of this attack, and when was the last severe attack. See Box 5.11 for acute severe asthma in children.

Features of severe asthma

- Cannot speak in whole sentences.
- RR >25 breaths/min.
- PR >110 beats/min.
- PEFR <50% of best or predicted.

Life-threatening asthma

- Silent chest, cyanosis, or feeble respiratory effort.
- Bradycardia, dysrhythmia, or hypotension.
- Exhaustion, confusion, or coma.
- O_2 saturations <92%, PO_2 <8kPa (60mmHg), PCO_2 normal or ↑.
- pH ↓.
- PEFR <33% of best or predicted.
- *Rule out airway obstruction*: foreign body, epiglottitis, mediastinal mass.

Immediate management

- Sit the patient up and give high-flow O_2.
- Give salbutamol 5mg or terbutaline 10mg by O_2-driven nebulizer. (Alternately give 10 puffs of salbutamol 100 micrograms via a spacer and repeat every 10–20min as necessary.)
- Give hydrocortisone 100mg IV or prednisolone 40–60mg oral.
- Do oximetry, CXR, PEFR.

If there is no improvement or there are signs of life-threatening asthma

- Add ipratropium 0.5mg to the nebulized salbutamol.
- Give aminophylline 5mg/kg by IV infusion over 20min, but avoid or use with great caution in patients already taking oral aminophylline.
- Contact an anaesthetist about possible emergency intubation if patient continues to deteriorate.

If the patient is improving continue with

- O_2 (high flow), aiming for O_2 saturation >92%.
- Prednisolone 40–60mg oral od or hydrocortisone 100mg IV qds.
- Salbutamol 5mg nebulized 4–6hrly and as required.

If the patient is not improving

- Continue with O_2 and steroids.
- Nebulized salbutamol 5mg up to every 15–30min until bronchospasm is relieved.
- Ipratropium 0.5mg qds.
- IV magnesium 1.2–2g single dose over 20min if bronchodilator not working.
- Intubation if exhausted.

Monitoring response to therapy

- PEFR 15–30min after treatment and at least 6hrly.
- Maintain SaO_2 >92% with supplemental O_2.
- Recheck ABG to monitor potential respiratory failure.

On discharge from hospital

The patient should have been:

- Stable on discharge medication for 24h and have had their inhaler technique checked and recorded.
- PEFR >75% of best or predicted and PEFR diurnal variability <25% (no nocturnal dipping).
- Treatment initiated with high-dose inhaled steroids to cover tapering oral steroid therapy.
- Follow up in 1wk and provide emergency plan.

Box 5.11 Paediatric note

Acute severe asthma in children >2yrs includes those with: O_2 saturation <92%, PEFR 33–50% of best or predicted, too breathless to talk, using accessory muscles and:

- *Pulse*:
  - >140 beats/min in children 2–5yrs.
  - >125 beats/min in children >5yrs.
- *Respiration*:
  - >40 breaths/min aged 2–5yrs.
  - >30 breaths/min aged >5yrs.

Life-threatening features include: O_2 saturation <92%, silent chest, cyanosis, poor respiratory effort, hypotension, exhaustion, agitation, and confusion. PEFR <33% predicted.

Management is initially with O_2, bronchodilators (salbutamol first line) and steroids.

- Nebulizers repeated in acute severe asthma every 20–30min.
- Ipratropium bromide 250 micrograms/dose (nebulized) can be effective in acute severe asthma, given frequently in the first few hours of admission (can be mixed with salbutamol). It should then be weaned to 4–6hrly.
- Give prednisolone early in acute asthma attacks (20mg oral prednisolone 2–5yrs, 30–40mg >5yrs). Course usually 3d. Repeat dose if the child vomits, or give IV hydrocortisone if necessary.
- Seek help for further management and parenteral therapy (IV salbutamol or aminophylline may be used).

Chronic obstructive pulmonary disease

This is a chronic progressive disease of the airways and alveoli, which occurs in smokers, ex-smokers, and non-smokers exposed to smoke or high levels of indoor air pollution.

Pathology

Inhalation of smoke → neutrophil inflammatory response in the airways which overcomes the protective effects of pulmonary protease inhibitors and → chronic bronchial inflammation and airway damage. Lung defences are ↓ by smoke → recurrent respiratory infections and bacterial colonization of the proximal airways. Bronchial mucosal gland, hyperplasia, and hypertrophy → excessive mucus secretion and airway thickening and narrowing → chronic productive cough, often seasonal and worse in winters. Alveoli are particularly damaged in emphysema → loss of lung units and over-distension of the remaining alveoli → compression of the terminal bronchioles → further airway obstruction.

Clinical features

Patients with COPD experience chronic productive cough, recurrent respiratory infections, and/or exertional dyspnoea. PFTs ↓ after respiratory infections, and may take weeks to recover. Minor respiratory infections may → respiratory failure and necessitate hospitalization. Patients are often wheezy, tachypnoeic, and use accessory muscles during exacerbations. In advanced cases patients may be plethoric, cyanosed, and have cor pulmonale. Type 1 (hypoxic, normocapnic) or type 2 (hypercapnic) respiratory failure is common. Confusion, drowsiness, and flapping tremor indicates CO_2 retention.

Management

Stopping smoking is essential (see Box 5.12 for advice to smokers). Long-acting bronchodilators provide relief. Inhaled corticosteroids ↓ exacerbations and ↓ the rate of lung function deterioration. Combination inhalers are effective; a spacer device improves delivery. Tiotropium once daily provides further symptomatic relief if available. Chest physiotherapy and mucolytics may help in clearing mucus and ↑ respiratory muscle strength.

In exacerbation

Oral steroids and antibiotics are helpful, but carry a high risk of steroid side effects (proximal muscle weakness, obesity, osteoporosis, skin bruising, etc.). In acute exacerbation, NIV can be life-saving and full ventilation often causes difficulty in weaning.

O_2 therapy should be closely monitored; high concentrations of O_2 may → CO_2 retention and narcosis. Home and portable O_2 therapy helps many patients—long-term oxygen therapy (Box 5.13) is life-prolonging in chronically hypoxic patients, but not often available in LMICs.

Box 5.12 Advice to smokers regarding smoking cessation

- *Preparation*: make a positive decision and list reasons for quitting. Get the support of family/friends. Set a target date. Recognize the difficulty. Most relapses occur in the 1st week after quitting.
- *Switch brands*: to one that is distasteful and low in tar/nicotine.
- *Cut down the number of cigarettes*: smoke only half of each cigarette. Postpone the first cigarette of each day by 1h. Smoke only during odd or even hours of the day. Remember cutting down is not a substitute for quitting.
- Do not smoke automatically, do not empty ashtrays.
- *Make smoking inconvenient*: buy one packet/cigarette at a time.
- *Make smoking unpleasant*: only smoke alone.
- *Prepare for the target day*: practise going without cigarettes.
- *On the day of quitting*: throw away all cigarettes and matches; hide ashtrays and lighters. Make a list of things you want to buy, price them in terms of cigarettes, and put the money aside to buy them. Keep busy on the target day. Remind family/friends about the day.
- *Immediately after quitting*: develop a clean, fresh, non-smoking environment. Go to places where smoking is not allowed.
- *Avoid temptation*: avoid situations you associate with smoking; socialize only where smoking is not allowed.

Box 5.13 Oxygen therapy

- If the patient has a PaO_2 <8kPa on air, give a trial of O_2 at 2L/min via a mask. Recheck ABG after 1h.
- If there is no ↑ in $PaCO_2$, ↑ the O_2 to 4L/min and recheck ABG after another hour. If you do not have blood gases, observe carefully for confusion, cyanosis, or flap.
- If the patient is not CO_2 retaining, they may have O_2 therapy without risk.
- If CO_2 does ↑, ↓ O_2 delivery to the level before which CO_2 was retained. Balance the risks of hypoxia and acidosis.
- At this point, if available, consider NIV via mask (e.g. bi-level positive airway pressure) to improve hypoxia and acidosis.

Bronchiectasis

Long-standing damage and dilatation of bronchi and bronchioles → inflammation and accumulation of infected mucus. Persistent infection in bronchiectatic airways with *Haemophilus influenza*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Pseudomonas aeruginosa* → clinical symptoms.

Aetiology

Most cases are 2° to inadequately treated pneumonia, pulmonary TB, TB lymph node disease, necrotizing pneumonias, whooping cough, foreign body inhalation, and allergic bronchopulmonary aspergillosis (proximal bronchiectasis). In developed countries, congenital conditions (e.g. cystic fibrosis, Kartagener's syndrome, or hypogammaglobulinaemia) are common.

Clinical features of bronchiectasis

Depending on the severity, patients may produce large volumes (several cupfuls) of mucoid or purulent sputum daily. In milder disease, patients may be asymptomatic between exacerbations. Fever, haemoptysis, and chest pain are features of exacerbation, esp. when infection spreads to the lung parenchyma → bronchopneumonia. Chronic sinusitis and otitis media may be associated. Clubbing is prominent, expiratory crackles with occasional wheezes are heard in the lungs.

Complications Recurrent episodes of pneumonia, hypoxia, and respiratory failure, massive haemoptysis, 2° amyloidosis, brain abscesses, and arthropathy.

Diagnosis

Largely based on the history and clinical features. Bronchiectatic cysts with fluid levels and 'tram lining' may be seen on CXRs, but CT scans are far more accurate. Airways obstruction and reversibility can be measured by PFTs to determine the usefulness of bronchodilators. Sputum should be cultured frequently if possible to choose appropriate antimicrobial therapy for exacerbations.

Management

- Physiotherapy esp. during acute exacerbations. Patients should be taught postural drainage and deep breathing/coughing exercises.
- Underlying conditions will require separate and continuous treatment. Focal disease with severe recurrent symptoms may be suitable for surgical resection, but CT often shows bronchiectasis is widespread and bilateral, which rules out surgery.
- Severe haemoptysis can be life-threatening → angiographic embolization or surgical resection in specialist centres.
- Airways obstruction requires bronchodilators and hydration.
- Broad-spectrum antibiotics (e.g. co-amoxiclav) are indicated as soon as the patient is symptomatic with purulent sputum. Continue for 1–2wks.
- *Pseudomonas* colonization requires use of fluoroquinolones or IV ceftazidime or aminoglycosides—depending on sensitivities.
- If patients need frequent repeated courses of antibiotics, then use three or four oral antibiotics (amoxicillin, erythromycin, chloramphenicol, doxycycline) in rotation.

Prevention Hib, pneumococcal, and influenza vaccination. Early identification and treatment of TB and whooping cough.

Lung cancer

More than 95% of cases occur in smokers and is related to the quantity and duration of exposure to cigarette smoke ('pack-years'). Most patients are incurable, hence, prevention is essential.

Clinical features of lung cancer

Patients may be asymptomatic until late, then have:

- Pulmonary features: persistent cough or alteration in the previous chronic cough; haemoptysis; chest pain; dyspnoea. Distal pneumonia, pleural effusions, localized wheezing, or stridor.
- Local/mediastinal invasion → vocal cord paralysis, Horner's syndrome, superior vena cava obstruction, chest wall invasion, bony pains, brachial plexus involvement, dysphagia, and pericardial effusion.
- Metastatic spread → symptoms and signs affecting brain, liver, adrenal, skin, and bones (esp. ribs, spine, and femoral). Lymph node involvement is common esp. mediastinal and supraclavicular.
- Systemic symptoms → fatigue, lassitude, anorexia, marked ↓ weight. Fever may occur without infection.
- Endocrinopathies → SIADH, hypercalcaemia (from secretion of parathyroid hormone (PTH)-like substances or from bony metastases). Ectopic adrenocorticotrophic hormone (ACTH) production, gynaecomastia, and testicular atrophy can also occur.
- Others: clubbing is common, occasionally severe, with hypertrophic pulmonary osteoarthropathy. Neuromuscular syndromes (e.g. Lambert–Eaton syndrome) are rare.

Diagnosis

Based on CXR or CT imaging, which shows a mass, collapse/consolidation or invasive disease; CT is also useful in staging the disease. Histology is obtained from a biopsy/cytology at bronchoscopy or BAL, fine needle aspirate cytology (FNAC), CT-guided or open biopsy. The yield from sputum cytology is low; pleural fluid cytology is useful in patients with disseminated lung cancer or mesotheliomas. In many LMICs, bronchoscopy is possible, but histology is difficult to obtain. In such cases, consider treatable alternative diagnoses (e.g. TB).

Management

Surgery is often impossible because of spread or coexistent COPD. <20% of patients with localized non-small cell disease (Box 5.14) may be cured by surgery. Palliative chemotherapy and radiotherapy both prolong life and improve complications such as haemoptysis, superior vena cava obstruction, and recurrent pleural effusions. Patients with small cell cancer generally have disseminated disease and palliative chemotherapy and radiotherapy can extend and improve quality of life and manage complications.

Prevention Anti-smoking campaigns benefit patients and those exposed to passive smoke. ↓ chemicals and dust in the work environment.

Box 5.14 Lung cancer: tumour types

- *Squamous cell carcinoma*: tumours have a medium rate of growth and often present with obstruction. Metastatic spread is common (80% at presentation).
- *Small cell (oat cell) carcinoma*: fast-growing tumours that often present with disseminated disease. They may secrete hormones.
- *Adenocarcinoma*: includes bronchoalveolar cell carcinoma; the most common peripheral tumour, it may produce mucin and can surround associated bronchi, stenosing the lumen. May not be smoking related.
- *Large cell carcinoma*: large, necrotic, pleomorphic, mucin-producing tumours; frequently peripheral and locally invasive. Metastatic spread is common, survival rates post surgery are good.
- *Carcinoid tumours*: unrelated to smoking and occur in a younger age group. May be benign adenomas or malignant. Most occur in proximal airways.
- *Metastases*: often from primaries in the breast, colon, kidney, prostate, and lung. Less often choriocarcinoma, testicular cancer, sarcomas, or melanoma.
- *Mesotheliomas*: malignancies of the pleural space caused by exposure, often remote, to asbestos. Spread is local, but rarely may metastasize.

Interstitial lung disease

Painless progressive shortness of breath may indicate interstitial lung disease (ILD). ILD is uncommon, and rarely treatable.

Clinical features

Careful history taking may define a risk factor for pulmonary fibrosis, e.g. mining, asbestos exposure. Clubbing is common; fine inspiratory crackles may be heard at both bases, or there may be no signs at all.

Investigation with CXR may show fine interstitial shadowing bilaterally or very little change in early disease. High-resolution CT if available will detect early disease, and PFTs will show ↓ gas transfer. In advanced ILD, clinical signs will be obvious, CXR abnormality will be marked and the patient will become hypoxic on minimal exertion.

Differential diagnosis

The classification of ILD is based on CT appearance and histology, both of which have limited availability. Occupational lung diseases are diagnosed by the history, but most ILD cases will not have an obvious cause. Sarcoidosis may be underdiagnosed.

Management

In resource-poor settings, palliation of symptoms is very difficult and treatment is impossible. Exacerbations due to infection can be treated, as can CCF. Steroids have limited benefit, and opiates are useful to control breathlessness.

Prevention

Control of industrial exposures is rudimentary in resource-poor countries, and exposures are often high in the absence of protective equipment. Prevention of occupational lung disease is best achieved with education and provision of better equipment.

Acute respiratory distress syndrome

Any severe infection or illness can be complicated by non-cardiogenic pulmonary oedema.

Aetiology

Burns, infection, surgery, trauma, pancreatitis, or poisoning can all → extensive pulmonary inflammation. Inflamed lung parenchyma then becomes leaky and fluid exudate fills the alveolar space.

Clinical features

Severely ill patients become markedly hypoxic over a short period of time (<1wk) despite adequate circulation and Hb. Examination shows bilateral poor air entry, fine crackles, or large airway noise. CXR shows marked bilateral shadowing → 'white out'.

Management

ARDS is very hard to manage, even in ICUs. Mechanical ventilation is essential. Treatment of the underlying diagnosis offers a chance of recovery, with organ support as can best be managed in the interim. Steroids are often tried but not usually helpful.

Pulmonary embolism

Risk factors for venous thrombosis are ↑ coagulability, stasis, and damage to the vascular endothelium. Most PEs occur as a result of migration of thrombi of recent onset from the deep veins of the leg or pelvis → pulmonary venous vasculature. Embolism from mural intracardiac thrombi and right-sided endocarditis may also occur. Septic thrombophlebitis due to infected central lines or IV drug abuse is ↑ common.

- Oral contraceptives and pregnancy ↑ coagulability.
- Young patients with no underlying risk factors may present with severe thrombotic disease due to congenital or acquired thrombogenic states (protein C, S, antithrombin III deficiency, antiphospholipid antibody syndrome, etc.).
- Pregnancy or recent surgery and protracted immobility after injury/travel ↓ venous return.
- In LMICs, severe dehydration (e.g. diabetic ketoacidosis), trauma, and obstetric emergencies may → PE due to a lack of prophylactic heparin.

Clinical features

Most patients will have minor and subacute symptoms with tachypnoea, mild dyspnoea, a cough, and occasionally low-grade fever. Some report a sudden onset of pleuritic chest pain and shortness of breath. In a few patients, haemoptysis indicates pulmonary infarction. If the diagnosis is missed, repeated emboli will occur. In patients with showers of emboli over years, pulmonary hypertension and cor pulmonale may ensue and patients may present with CCF and marked exertional dyspnoea. In cases of massive PE the patient has circulatory collapse and may die acutely.

On examination, respiratory findings are sparse, but hypoxia with a normal CXR suggests the possibility of a PE. A DVT may be present. Investigations: a CT pulmonary angiogram is most accurate. Evidence of PE also from: CXR, ECG (any abnormality, particularly tachycardia, R axis deviation, or RBBB; classical S1, Q3, T3 is rare), ventilation/perfusion scan, Doppler USS of the legs and D-dimer levels. These tests are useful in both the confirmation and exclusion of DVTs and PEs.

Management

Anticoagulate with IV heparin or with twice-daily low-molecular-weight heparin (expensive). The diagnosis of PE is not easy to make and so the Wells score (Box 5.15) is used to define high, medium, and low risk of recurrent PE. Using this score, a clinical decision can be made to institute oral anticoagulation with warfarin. Once a target INR of 2.5–3.0 is maintained for 48–72h then heparin can be safely discontinued. It is problematic, however, to manage warfarin anticoagulation where INR cannot be measured and the risk of haemorrhage is significant. In acute massive PE, thrombolysis with streptokinase may be useful provided the diagnosis can be confirmed.

Box 5.15 The Wells score

- Clinically suspected DVT: 3.0 points.
- Alternative diagnosis less likely than PE: 3.0 points.
- Tachycardia: 1.5 points.
- Immobilization/surgery in previous 4wks: 1.5 points.
- History of DVT/PE: 1.5 points.
- Haemoptysis: 1.0 points.
- Malignancy (treatment for <6mths, palliative): 1.0 points.

Traditional interpretation

Score >6.0	High (probability 59% based on pooled data).
Score 2.0–6.0	Moderate (probability 29% based on pooled data).
Score <2.0	Low (probability 15% based on pooled data).

Alternate interpretation

Score >4	PE likely. Consider diagnostic imaging.
Score ≤4	PE unlikely. Consider D-dimer to rule out PE.

Pneumothorax

Air leak into the pleural space → collapse and sometimes compression of the underlying lung. A rapid ongoing accumulation of air can occur with each bout of coughing → tension pneumothorax; relief of the tension pneumothorax is an emergency. A small or moderate pneumothorax may be sufficient to cause respiratory failure in a patient with pre-existing lung disease. Pneumothorax may be asymptomatic in an otherwise healthy patient.

Causes

Spontaneous/primary pneumothorax

Common in tall and thin men with no pre-existing lung disease. 20% recur after first episode and 65% after a second episode.

Secondary pneumothorax

Occurs in patients with scars of previous TB or in patients with active TB, often cavitary. Also common in patients with COPD, and can complicate severe necrotizing lung infections such as staphylococcal pneumonia, aspiration pneumonias and PCP.

Traumatic pneumothorax Occurs from penetrating injuries, e.g. stabbing or road traffic accident.

Iatrogenic pneumothorax May be a complication of central line insertion, transbronchial lung biopsy, or high-pressure mechanical ventilation.

Clinical features

Most patients will experience sudden-onset pleuritic chest pain and dyspnoea. Hyper-resonance to percussion is accompanied by ↓ movement and ↓ or absent breath sounds on the affected side. Breathing is generally shallow because of pleuritic pain. A tension pneumothorax → mediastinal displacement away from the pneumothorax → severe tachypnoea, dyspnoea, hypoxia, and shock.

Management

- *Small pneumothoraces* (on CXR pneumothorax occupies <15% of hemithorax) in asymptomatic, otherwise healthy, individuals need no treatment other than observation. Follow-up X-rays should demonstrate gradual absorption of the pneumothorax (1% of lung area per day).
- *Symptomatic p*neumothoraces require aspiration. A flexible venous cannula is placed into the pleural space (above a rib in mid-axillary line) and a three-way tap attached. A large syringe is used to draw air out of the chest and expelled through tubing held under water. Count the volume of air withdrawn and stop when resistance is felt on the cannula. Aspiration is suitable for iatrogenic pneumothoraces, because these are unlikely to recur.
- If aspiration fails or if >2L of air is freely withdrawn it is likely that a bronchopleural fistula exists and an intercostal chest drain should be placed. Use the fifth/sixth intercostals space in the mid-axillary line. Safest method is to place pigtail drains by Seldinger technique under US guidance. If not practicable, use traditional blunt dissection to place a tube drain with an underwater seal. Clamp the drain when stopped

bubbling for >24h; unclamp periodically to see if air has reaccumulated. Ideally repeat CXR, but if not possible, remove drain after >24h clamped if no recurrence.

- *Pleurodesis* may be required if pneumothorax fails to resolve despite 1–2wks of intercostal drainage and suction (Box 5.16).
- *Tension pneumothorax* is a medical emergency and requires the immediate placement of a wide-bore canula into the second intercostal space on the affected side. Air usually bubbles out in a rush and the relief is immediate. Intercostal tube drainage should follow.

Box 5.16 Pleurodesis

This procedure → sterile inflammation of the pleura and obliterates the pleural space by adhesions and fibrosis. It is painful and needs adequate analgesia: 20mL of 1% lidocaine is diluted with saline to 100mL and this is inserted into the chest tube which is then clamped. The patient is placed on their back, side, and chest to disperse the lidocaine and after this is drained off, 1–1.5g of tetracycline dissolved in 30–50mL normal saline, or 20mL of povidone-iodine 10% in 80mL normal saline, is inserted into the chest drain and the procedure repeated. The solution is kept in the chest for 3–4h and then drained off. The chest drain is maintained *in situ* until air ceases to bubble through it.

Chapter 6

Gastroenterology

Kelsey D.J. Jones

Disorders of the mouth and pharynx

Tooth decay and dental caries

Perhaps the world's most widespread chronic disease. Access to preventative dental care is often limited, so will generally present when symptomatic with pain, or with dental abscess where formal drainage or extraction of the affected tooth may be required. Where dental care is unavailable, Murray Dickson's *Where There Is No Dentist* is available online (🖱 http://www.hesperian.org).

Gingivitis

Simple gingivitis (gum swelling) is extremely common. Bleeding or swollen gums +/− bad breath → tooth loosening and loss (periodontitis). If unusually severe consider acute necrotizing ulcerative gingivitis caused by fusiform bacteria and spirochaetes, drugs (phenytoin, ciclosporin, nifedipine), diabetes, neutropenia, leukaemia, and vitamin C deficiency (scurvy).

Treatment Reinforce preventive oral health. Look for underlying cause if severe. Treat acute necrotizing ulcerative gingivitis with saline mouth washes, metronidazole + penicillin, and dental surgical input.

Gingivostomatitis and mouth ulcers

Acute gingivostomatitis (inflammation of the gums/oral mucosa with focal ulceration) may be caused by HSV, EBV, or enteroviruses.

Treatment Treat HSV gingivostomatitis with aciclovir.

Aphthous ulcers

Aphthous ulcers may be idiopathic or due to HIV; neutropenia; coeliac disease; Behçet's, Crohn's, or Stevens–Johnson syndrome; or vitamin B_{12} deficiency.

Treatment Topical protective emollients +/− local anaesthetic. Topical steroid (e.g. hydrocortisone 2.5mg oromucosal tablet or beclometasone inhaler applied directly to ulcers) may occasionally be required. Consider oral prednisolone or thalidomide for major aphthous ulceration in HIV. Consider biopsy of persistent ulcer(s) to exclude malignancy.

Cancrum oris (noma)

Polymicrobial and anaerobic infection rapidly progresses to gangrenous stomatitis with destruction of mouth and facial structures. Arises especially in young children who are severely malnourished. Acute management requires wound debridement and antisepsis, antibiotics (IV penicillin + metronidazole), and nutritional support. Later, surgical reconstruction is often needed to prevent lifelong disfigurement.

Oral candidiasis

Small, white mucosal flecks, best seen on buccal mucosa and palate, with surrounding erythema; the surface of the tongue may be uniformly white. Patient will be reluctant to take orally because of painful mouth. Common in HIV, and may extend down the oesophagus → painful dysphagia. Treat with nystatin. Nystatin dose in infants: 100,000 units qds (use dropper to place half of dose in each side of mouth and avoid feeding for 5–10mins).

In premature and low birth weight infants, use 100,000 units qds. In children and adults, use 400,000–600,000 units qds (half of dose in each side of mouth). Nystatin works by contact and little is absorbed; the liquid should be kept in the mouth as long as possible before swallowing. Continue until no symptoms for 48 h. Severe disease may require oral fluconazole, esp. if oesophageal involvement is suspected.

Oral hairy leukoplakia

Poorly demarcated, painless, raised, corrugated white patches on the side of the tongue or buccal mucosa. Cannot be scraped off (unlike *Candida*). Caused by EBV, very strongly associated with HIV infection.

Salivary gland hypertrophy

Causes include acute malnutrition, and diffuse inflammatory lymphocytosis syndrome in HIV.

Glossitis

Smooth, red, sore tongue. Occurs with iron, folate, vitamin B_{12}, and other B vitamin deficiencies. May be a manifestation of an underlying malabsorptive process.

Angular stomatitis

Occurs in iron-deficiency anaemia, HIV, and riboflavin deficiency.

Pharyngitis

Typically due to streptococci, viruses, or diphtheria, also seen in Lassa fever. In settings with high incidence of acute rheumatic fever, consider treating children (especially >3yrs) with sore throat with single-dose IM benzathine benzylpenicillin 1,200,000 units if >30kg, 600,000 units if <30kg, especially if lymphadenopathy but no rhinitis or rash.

Severe pharyngitis with spread to neck, thrombosis of internal jugular vein, +/– embolization of infected thrombus typifies necrobacillosis (Lemierre's disease)—treat with IV penicillin and metronidazole.

Malignant lesions of the mouth and pharynx

Incidence of oropharyngeal cancer is substantially ↑ in resource-limited settings. There is marked global variation both in the incidence rate and subtype. Buccal squamous cell carcinoma (associated with tobacco, chewing betel nut, +/– alcohol) and Burkitt's lymphoma (due to EBV infection) are common, especially in India, Southeast Asia, and tropical Africa. Nasopharyngeal carcinoma (also due to EBV infection) is common in the Far East and southern China. Malignant change may be preceded by leukoplakia and epithelial atrophy.

Optimal management and outcome require early diagnosis. Consider malignancy in chronic (>3wks), solitary lesions: examine for cervical lymphadenopathy, and biopsy lesion +/– lymph nodes. KS causes purple lesions, often on the hard palate. It is usually associated with HIV; treatment is with ART.

Dyspepsia, dysphagia, and reflux

Dyspepsia

Epigastric or retrosternal discomfort. May be periodic and associated with hunger, eating, specific foods, etc. Causes include:

- *Peptic ulcer disease (PUD)*: epigastric pain, nocturnal waking, and relief by eating food, drinking milk, or taking antacids.
- *Gastro-oesophageal reflux (GORD)*: retrosternal discomfort, heartburn, and regurgitation/acid brash. Worse lying flat or after large meals. May → persistent dry cough.
- *Dysmotility*: early satiety, bloating, and nausea.
- *GI tract parasites*: hookworm, *Taenia*, *Ascaris, Giardia*, *Entamoeba histolytica*.
- *Drugs*: e.g. NSAIDs, calcium antagonists, nitrates, pyrazinamide.
- *Malignancy*: suspect if age >45yrs and if progressive or accompanied by any of: anaemia, ↓ weight, anorexia, melaena, haematemesis, or dysphagia.

Management

- Stop: drugs that may be contributing, smoking, and alcohol.
- If no immediate concerns re: malignancy, consider a trial of antacids.
- Prevalence of *H. pylori* infection is extremely high regardless of symptoms in many resource-limited settings. Testing/treating are of uncertain benefit. Antimicrobial resistance risk may be high.
- Endoscopy is indicated if malignancy or PUD suspected.
- Stool microscopy if GI parasites suspected (although samples may be false negative and presence of parasites does not exclude other causes). See Colour Plates 5–8.

Dysphagia

Difficulty in swallowing. Odynophagia is pain on swallowing. Ask at what level the pain or blockage is felt, whether vomiting follows, and whether solids or liquids (or both) → symptoms. Causes include:

- *Malignancy*: carcinoma of the oesophagus, stomach, or pharynx.
- *Extrinsic compression*: mediastinal lymphadenopathy, lung carcinoma, retrosternal goitre, left atrial enlargement.
- *HIV associated*: candidiasis, CMV, HSV, severe aphthous ulceration.
- *Motility disorders*: achalasia, Chagas' disease, bulbar/pseudobulbar palsy (incl. bulbar poliomyelitis), diffuse oesophageal spasm, myasthenia gravis, syringobulbia, systemic sclerosis.
- *Benign strictures*: peptic stricture, ingestion of caustics, oesophageal web, iron-deficiency anaemia (Plummer–Vinson syndrome).
- *Pharyngeal pouch*.
- *Others*: trauma, foreign body (e.g. bezoar, swallowed fish or animal bone), anxiety (globus pharyngis).

History provides important clues (Box 6.1). Endoscopy +/− imaging (CT or barium swallow) are investigations of choice where available. In HIV, a trial of empirical oral fluconazole for 2wks for oesophageal candidiasis ↓ the need for endoscopy. Management depends on the underlying cause.

Box 6.1 Dysphagia: clues in the history

- *Dysphagic to solids but tolerates fluids?*
  - Suspect an oesophageal stricture (benign or malignant).
- *Dysphagic to solids and also to fluids?*
  - Suspect a motility disorder.
- *Is the dysphagia constant and painful?*
  - Suspect oesophageal candidiasis or a malignant stricture.
- *Is it difficult to initiate swallowing?*
  - Suspect bulbar palsy, esp. if swallowing causes cough.
- *Does the neck bulge or gurgle upon swallowing?*
  - Suspect pharyngeal pouch.
- *Is the patient HIV-infected?*
  - Suspect oesophageal candidiasis.

Gastro-oesophageal reflux disease

Heartburn and regurgitation with a bitter, acid taste, particularly when lying flat, are characteristic. May also → a chronic non-productive cough or wheezing.

Diagnosis

Usually clinical. Barium swallow may rule out an anatomical abnormality (e.g. hiatus hernia). Endoscopy may rule out malignancy and identify Barrett's oesophagus. Barrett's oesophagus requires aggressive treatment and follow-up endoscopy to screen for malignant change.

Management

Stop smoking, ↓ weight if obese, and raise the head of the bed ~15cm. If mild, advise antacids after meals and at bedtime. High doses of H_2 receptor antagonists or proton pump inhibitors are very effective.

Gastro-oesophageal reflux disease in children

Some degree of reflux is physiological in babies and will resolve spontaneously. Treat if symptoms (vomiting, discomfort, etc.) are severe or → ↓ growth. Review feeding history and consider smaller and more frequent feeds. If formula fed, may try a thickening agent. If unsuccessful, consider stepping up to trial an alginate therapy, and from there an H_2 receptor antagonist or proton pump inhibitor (PPI). Surgical treatment is *almost never* required. Be alert to important differentials:

- Bile-stained vomit (green) suggests intestinal obstruction and is a surgical emergency.
- Projectile vomiting is characteristic of pyloric stenosis (check bloods including pH and monitor).
- Non-GI causes of vomiting in babies include UTI and ↑ ICP.
- Consider cow's milk protein allergy in affluent settings.

Upper gastrointestinal bleeding

Assessment

Haematemesis and/or melaena (see Box 6.2 for causes) indicate upper GI bleeding. Ask about previous GI bleeds (esp. history of PUD, varices), liver disease, dysphagia, vomiting or ↓ weight, comorbidity, alcohol, and drugs. Look for signs of liver disease and portal hypertension. Rectal examination for melaena.

- *Mild to moderate bleed:* <60yrs pulse/BP normal, insignificant comorbidity, and Hb >10g/dL (unless chronic anaemia present).
- *Severe bleed*: age >60yrs, pulse >100 beats/min, systolic BP <100mmHg, Hb <10g/dL, significant comorbidity.

Management

- Protect the airway.
- IV access (two large-bore venous cannulae; central venous access to assist fluid resuscitation if severe).
- Blood for FBC, U&E, LFT, clotting, and cross-match.
- Give IV fluids to restore intravascular volume while waiting for blood (if required). In exsanguinating bleed, use O−ve blood.
- Correct clotting abnormalities (vitamin K, FFP, platelets).
- Do not *routinely* transfuse: excess transfusion → ↑ risk of rebleeding and mortality in European studies.
- Monitor vital signs closely. Catheterize bladder if severe bleed to monitor urine output.
- Consider urgent endoscopy, and notify surgeons of all serious bleeds on admission; keep patient nil by mouth until stable.
- High-dose IV PPI therapy (e.g. omeprazole 80mg bolus followed by infusion at 8mg/h for 3d) ↓ rebleeding but has little effect on mortality (adults).
- Further management depends on severity, response to initial treatment, diagnosis, and what is possible in a resource-limited setting.

Box 6.2 Causes of upper GI bleeding in adults

More common causes

- Peptic ulcer disease.
- Oesophageal varices.
- Malignancies.
- Reflux oesophagitis.
- Gastritis/erosions.
- Mallory–Weiss tear.
- Duodenitis.
- Drug related (NSAIDs, anticoagulants, steroids).

Rarer causes

- Portal hypertensive gastropathy.
- Angiodysplasia.
- Dieulafoy lesion.
- Bleeding disorders.
- Aortoenteric fistula.
- Haemobilia (bleeding from biliary tree).

Oesophageal varices

In portal hypertension, portosystemic shunts develop in the lower oesophagus → dilated oesophageal veins. Variceal bleeding occurs in 20–50% of cirrhotic patients, usually <2yrs of diagnosis. Mortality from first bleed is >50% and is related to severity of liver disease.

Common causes Liver cirrhosis, schistosomiasis, portal vein thrombosis, and Budd–Chiari syndrome (hepatic vein thrombosis).

Management of an acute variceal bleed

- Assess and resuscitate as for any upper GI bleed.
- *Protect airway*: may need intubation and ventilation if uncontrolled bleeding, encephalopathy, hypoxia, or aspiration pneumonia.
- *Control bleeding*: endoscopic variceal band ligation or sclerotherapy. Balloon tamponade with a Sengstaken–Blakemore tube may be used for emergency short-term control of bleeding (ideally, patient should be intubated and ventilated). If prompt endoscopy not possible, be cautious not to over-transfuse, as → ↑ portal pressures → rebleed.
- Correct clotting abnormalities (FFP, vitamin K (10mg IV), platelets).
- Variceal bleeding is associated with bacterial infection, so give antibiotics, e.g. IV ceftriaxone 1g od (complete a 5d course of antibiotics at least).
- Give terlipressin if available (2mg IV initially, then 1mg IV every 4h for 72h) and/or octreotide (50 micrograms/h IV for 2–5d).

Primary and secondary prevention of variceal bleeding

- Endoscopic variceal band ligation is effective if available; sclerotherapy also works.
- ↓ portal vein pressure with propranolol 40–80mg bd oral.
- Manage underlying cause, especially schistosomiasis—periportal fibrosis regresses after treatment. Advise to abstain from alcohol.

Acute abdominal pain

Priorities are to determine the (1) need for immediate resuscitation and treatment, (2) need for urgent surgery, and (3) cause of the pain, which may arise from many causes (Box 6.3). Thorough history and examination are essential. Repeated clinical examinations will help to identify patient with evolving signs where surgery may be required. Do not let a +ve test for malaria lead to complacency and missed peritonitis.

Patients who are likely to require urgent surgery

- Shocked.
- Sudden-onset severe pain.
- Acute abdominal distension.
- Widespread peritonitis with rigid abdomen.

Any combination of these features could arise from a perforated, ruptured, twisted, or infarcted viscus. If recent trauma, malaria, or EBV infection, consider rupture of the spleen. Remember that acute pancreatitis may cause these features but does not require surgery—check amylase.

Management

- Safeguard the airway, O_2 if required.
- FBC, U&E, LFT, Ca2+, clotting, amylase, culture, cross-match, blood gas.
- Pregnancy test for all women of childbearing age.
- Resuscitate with fluids or blood as appropriate. Anaesthesia ↓ BP, so resuscitate properly before taking to theatre—unless losing blood faster than it can be replaced (e.g. ruptured ectopic pregnancy, leaking abdominal aortic aneurysm).
- Insert NGT and keep patient nil by mouth.
- Consider erect CXR, AXR, +/– ECG.
- Broad-spectrum empiric antibiotics if infection suspected; rationalize therapy later in light of investigations and progress.

Box 6.3 Medical causes of acute abdominal symptoms

Abdominal

- Typhoid.
- Cholera.
- Yersinia.
- Abdominal TB.
- Pancreatitis.
- Fitz-Hugh–Curtis syndrome (Chlamydia).
- Urinary tract infection.
- Pyelonephritis.
- Herpes zoster.
- Irritable bowel syndrome.
- Viral haemorrhagic fevers.
- Testicular pathology.

Systemic

- Malaria.
- Diabetic ketoacidosis.
- Thyroid storm.
- Addisonian crisis.
- Porphyria.
- Opiate addiction.
- Sickle cell crisis.
- Polyarteritis nodosa.
- Henoch–Schönlein purpura.
- Lead poisoning.

Thoracic

- Myocardial infarction.
- Pneumonia.

Diagnostic approach

Determine the location of pain or where it is worst (Fig. 6.1), and the type of pain:

- *Constant pain*: often due to inflammation. Look for clinical features of localized peritonitis. Consider an abscess if swelling and high/swinging fever (may see a 'sentinel loop' on plain AXR due to localized ileus).
- *Colicky pain*: due to muscular spasm of a hollow viscus, e.g. ureter, salpinx, gall bladder. Intestinal obstruction → colic, distension, absolute constipation, and tinkling/absent bowel sounds.

PV examination may identify gynaecological causes of acute abdomen (e.g. tenderness with salpingitis). Blood and urine tests (as previously mentioned) may be helpful but imaging (plain films, USS, and CT, depending on local access and availability) often helps to make a diagnosis.

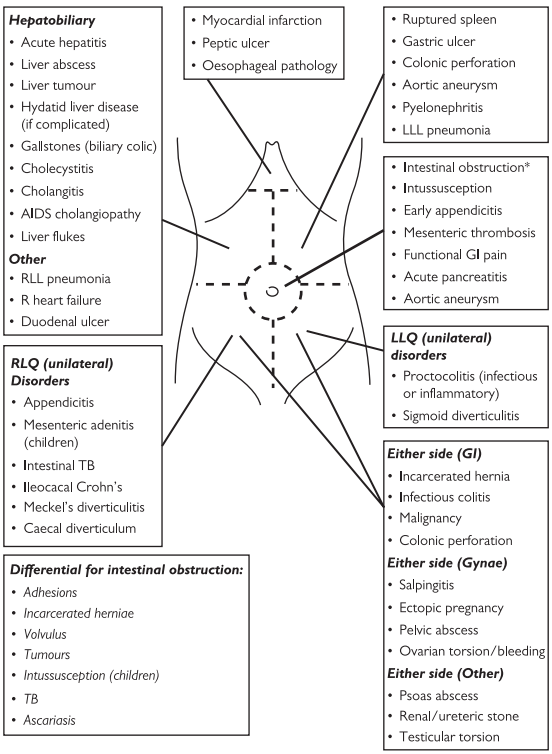


Fig. 6.1 Causes of acute abdominal pain by location.

Acute diarrhoea

Diarrhoea is defined as the passage of ≥3 loose or liquid stools in 24h, or more frequently than normal for the patient. Breastfed babies may ordinarily have loose stool, and caregiver perception of a change in stool is important. Most diarrhoea is caused by infection (Box 6.4), has an acute onset, and is categorized by stool appearance as acute watery diarrhoea or acute bloody diarrhoea (dysentery). Infectious diarrhoea usually resolves within a week; diarrhoea for >14d is termed persistent diarrhoea, and is more likely to result from a non-infectious cause.

Disease burden

In 2015 there were 2.4 billion diarrhoeal illnesses → 1.3 million deaths, 40% of which were of children <5yrs. Diarrhoea in childhood is associated

Box6.4 Aetiology of diarrhoea

Acute diarrhoea with blood (dysentery)

- Bacillary dysentery (shigellosis).
- Amoebic dysentery.
  - Enterohaemorrhagic *E. coli*.
- *Balantidium coli* enterocolitis.
  - *Campylobacter* enterocolitis.
- Massive *Trichuris* infection.
  - *Salmonella* enterocolitis.
  - S. *mansoni* or S. *japonicum*.
  - *Clostridium difficile* associated (pseudomembranous) colitis.
- CMV in immunosuppressed esp. advanced HIV
  - *Yersinia* enterocolitis.
- Non-infectious causes include IBD, colorectal cancer or polyps, ischaemic colitis.

Acute diarrhoea without blood

The causes listed above can cause non-bloody diarrhoea.

Systemic infections

- Malaria, especially *P. falciparum*. Sepsis.

Viruses

- Rotavirus.
- Astrovirus.
- Enteric adenovirus.
- Noroviruses.
- Sapoviruses.

Bacteria

Early or mild shigellosis; *Salmonella* or *Campylobacter* infections.
Enterotoxigenic *E. coli* (ETEC) (e.g. traveller's diarrhoea).
Enteropathogenic *E. coli* (EPEC).
Enteroaggregative *E. coli* (EAEC).
Enterotoxin-producing strains of *Staphylococcus aureus*

with growth faltering, malnutrition, cognitive impairment, and ↓ immunity. Breastfeeding confers protection; diarrhoeal incidence ↑ in the months following weaning. Lack of access to safe water, inadequate sanitation, and poor hygiene are important risk factors.

Clinical assessment of children with diarrhoea

Key questions:

- *Is this child shocked?*
  - Children with diarrhoea may develop hypovolaemic and/or septic shock. Assess airway, breathing, and circulation (pulse, BP, peripheral perfusion). Resuscitate as described (➲ p. 6).
- *Is this child severely dehydrated?*
  - Diarrhoea with any two of (1) lethargy, (2) sunken eyes, (3) very slow skin pinch: IV fluids are usually indicated (➲ p. 6). See Fig. 6.2.
- *Does this child have severe acute malnutrition (SAM)?*
  - Measure mid-upper arm circumference on arrival in children <5yrs. Check for peripheral oedema (kwashiorkor). Children with SAM require different resuscitation/rehydration strategies; all require antibiotics (➲ p. 11).
- *Could this child have HIV?*
  - HIV infection ↑ diarrhoeal morbidity and often → persistent diarrhoea from multiple causes.
- *Are the stools bloody?*
  - Acute bloody diarrhoea is more likely to have a bacterial cause than acute watery diarrhoea, esp. where there is dysentery: frequent small bloody or mucoid stools with abdominal pain and fever. Antimicrobials are indicated.
- *Is the diarrhoea profuse and watery?*
  - Consider cholera which can → severe dehydration, shock, and electrolyte disturbances. See specific management (including antimicrobial treatment) of cholera (➲ p. 253).
- *Is there another pathology or problem as well?*
  - Pneumonia, malaria, and sepsis are serious but treatable. Consider hypoglycaemia if lethargic. Consider intussusception in infants with bloody stool, esp. if paroxysmal abdominal pain.

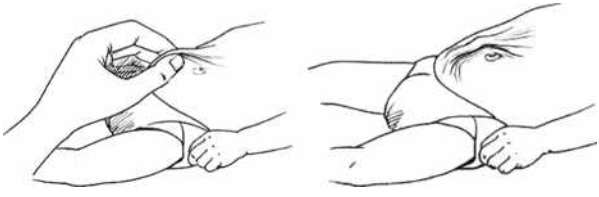


Fig. 6.2. Skin pinch to assess skin turgor. Pinch skin midway between umbilicus and flank, then release skin to observe how quickly it goes back. Skin pinch returns very slowly (≥2 seconds) in severe dehydration due to reduced skin turgor. Reproduced with permission from Management of the Child with a Serious Infection or Severe Malnutrition with permission from WHO.

Medical management of children with acute diarrhoea

Detect and manage dehydration

Determine whether *severe dehydration* (requiring IV rehydration: WHO treatment plan C), *some dehydration* (requiring inpatient/observed oral rehydration: WHO treatment plan B), or *no dehydration* (home-based care: WHO treatment plan A) (Box 6.5).

Provide zinc supplementation

Zinc deficiency is widespread among children living in areas with high diarrhoeal burden (🔗 http://www.izincg.org). Zinc supplementation for children with acute diarrhoea ↓ duration of disease and ↓ future episodes. Give 20mg od if ≥6mths, 10mg od for infants <6mths. Provide 14d course, to begin once tolerating oral intake.

Provide antimicrobials if indicated

Inappropriate antibiotics ↑ cost of treatment, risk of adverse reactions, and development of resistance in the community. Restrict antibiotics to:

Acute diarrhoea with blood

Treat *Shigella* according to local sensitivities, e.g. ciprofloxacin (15mg/kg bd for children, 500mg bd for adults, for 3d). Alternatives: ceftriaxone, cefixime, azithromycin.

Cholera with severe dehydration

Treat *Vibrio cholerae* according to local sensitivities. Azithromycin (20mg/kg for children, 1g for adults, single dose), ciprofloxacin (15mg/kg bd for 3d for children, single 1g dose for adults), doxycycline (adults only, 300mg single dose) or tetracycline 500mg qds for adults, for 3d) are alternatives.

Prevent dehydration by giving more fluids than usual

Encourage as much oral fluid intake as possible. ↑ frequency and length of breastfeeds. Provide a fluid that contains salt (e.g. oral rehydration solution (ORS), or soup with salt added), as well as plain water or fluids that do not. Avoid excessively sweetened fluids (including commercial juices) and carbonated drinks.

Continue feeding to prevent malnutrition

Continue usual diet during diarrhoea and ↑ intake afterwards. Do not withhold food where there is appetite. Always continue breastfeeding. Offer little and often, aim for high energy and micronutrient content, and foods rich in potassium, e.g. bananas, coconut water, fresh fruit juice (Box 6.6). There is no evidence to support routine avoidance of any particular foods.

Consider vitamin A deficiency

- Diarrhoea ↓ absorption but ↑ requirement for vitamin A. Where vitamin A deficiency is prevalent, children with diarrhoea are at risk of developing acute eye disease. Routinely examine for corneal clouding and conjunctival lesions. Treat if deficiency suspected clinically, if malnourished, or if recent measles.
- 50,000IU vitamin A for children <6mths; 100,000IU for children 6–12mths; 200,000IU for children >12mths. Give dose on days 1, 2, and 14 (or at discharge).

Box 6.5 Determining type and degree of dehydration

Dehydration due to diarrhoea is a major cause of childhood death. Volume of fluid lost in stool in 24h can vary from 5mL/kg to >200mL/kg. Electrolyte loss (sodium, potassium, bicarbonate) also varies. Hypo- or hypernatraemia may occur, exacerbated by rehydration with inappropriate solutions: hyponatraemia due to ↑ water ingestion without sodium replacement; hypernatraemia due to ingestion of hypertonic fluids (e.g. sweetened fruit juice, formula milk) that → osmotic fluid loss and do not adequately replace water losses. Either can present with convulsions. Measure sodium in severely dehydrated children to help choose IV fluids, and if there are any signs of encephalopathy.

- *Severe dehydration* (>10%)—two or more of:
  - Lethargic/unconscious.
  - Sunken eyes.
  - Unable to drink or drinks poorly.
  - Skin pinch goes back very slowly (>2s).
- *Some dehydration* (5–10%)—two or more of:
  - Restless/irritable.
  - Sunken eyes.
  - Drinks eagerly, thirsty.
  - Skin pinch goes back slowly.
- *No dehydration* (<5%)—fewer signs than above-listed.

These clinical signs are somewhat subjective. Assess skin turgor with a skin pinch over the abdomen. Caregiver impression of sunken eyes is usually accurate. Assessment of dehydration is children with SAM is particularly difficult, since clinical features of severe wasting and/or sepsis mimic those of dehydration.

Consider the need for investigations

Laboratory investigations are not usually indicated in uncomplicated acute diarrhoea. If prolonged rehydration is required, electrolytes and FBC are helpful. Exclusion of alternative or additional infections (e.g. malaria) is a priority. Stool culture rarely alters clinical management; stool microscopy should only be done by properly trained and competent microscopists. (See Colour Plates 5–8).

Management of severe dehydration: WHO treatment plan C

- Assess for features of shock (for management see ➲ p. 6) and SAM (for management see ➲ p. 235).
- Weigh the child if possible.

If IV therapy is possible on site

- Give 100mL/kg Ringer's lactate (or 0.9% saline) IV as follows:
  - Age <1yr: 30mL/kg over 1h, then 70mL/kg over 5h.
  - Age 1–5yrs: 30mL/kg over 30mins, then 70mL/kg over 2½h.
- Add oral ORS at 5mL/kg/h once child able to drink.
- Reassess:
  - Every 15–30mins during rehydration, consider ↑ infusion rate if not improving.
  - On completion of the treatment plan, reassess hydration status and choose appropriate plan (A, B, or C) for ongoing care.

Box 6.6 Poverty and the gut

The intestinal mucosal surfaces are 1° sites of interaction and interchange with our surroundings. Mucosal structure and function are shaped by experience of the environment, especially the hardships of living in poverty. Inadequate nutrition, contaminated water supplies, an inability to hygienically dispose of waste, and chronic exposure to environmental toxins → the development of a small intestinal inflammatory enteropathy called environmental enteric dysfunction (EED). EED is extremely common in many impoverished populations. Overlapping with inflammatory enteropathies of SAM and HIV, EED is an 'iceberg' of intestinal ill-health with acute diarrhoeal diseases at its tip. Although EED is not associated with acute symptoms, its chronic inflammation may → ↓ growth and development in childhood with great public health significance. 'Tropical sprue' is a poorly defined syndrome associated with diarrhoea that has many similar features to EED. EED may be partly protective when living with very high pathogen burden, but antimicrobial treatment is ineffective. See Fig. 6.3 for distribution of tropical sprue. Diarrhoeal infections are potentially complex acute-on-chronic illnesses with multisystem involvement and long-term consequences.

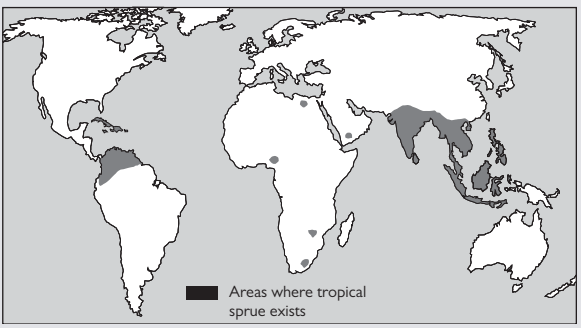


Fig. 6.3 Distribution of post-infective malabsorption (tropical sprue).

If IV therapy is not possible on site

- Refer to hospital if <30mins away, giving ORS for the journey.
- Consider enteral rehydration if far from hospital care:
  - 20mL/kg/h of ORS orally or via NGT for 6h.
  - Reassess hourly.
  - ↓ rate if repeated vomiting or abdominal distension.
  - Send for IV therapy if no improvement after 3h.

Management if some dehydration: WHO treatment plan B

- Assess for features of SAM (➲ p. 236).
- Weigh the child if possible.

- Provide ORS:
  - Aim to give 75mL/kg over 4h as frequent small sips. May give more if the child wants to take it.
  - If weight is not available base 4h target volume on age:
    - <4mths (<6kg): 200–400mL.
    - 4–12mths (6–10kg): 400–700mL.
    - 12–24mths (10–12kg): 700–900mL.
    - 2–5yrs (12–19kg): 900–1400mL.
  - If the child vomits, wait 10mins then continue more slowly.
- Continue breastfeeding whenever the child wants.
- Reassess at 4h and choose appropriate plan (A, B, or C) for ongoing care.
- Once no longer dehydrated—feed. All children over 4–6mths should be given some food before going home.

No dehydration: WHO treatment plan A (home-based care)

Aim to prevent dehydration and malnutrition by ensuring caregivers are able to attend to the *four rules of treatment plan A*:

1. **Give more fluids than usual, to prevent dehydration:**
   - Breastfeed frequently and for longer at each feed.
   - If exclusively breastfed, offer ORS or clean water in addition to breastmilk. If not exclusively breastfed, give mix of fluids some that that do, some that don't, contain *salt*.
   - Aim to give extra fluid after each loose stool: 50–100mL if <2yrs; 100–200mL if ≥2yrs (or as much as the child wants).
   - Give supply of ORS for home. Show how to prepare and administer it.
2. **Give supplemental zinc (10–20mg od) for 10–14d:**
   - Show how to administer. May be dissolved in clean water, ORS, or expressed breastmilk for infants.
3. **Continue to feed the child, to prevent malnutrition.**
4. **Take the child to a health worker if there are signs of dehydration or other complications:**
   - Ensure caregivers know how to get help if the child (1) develops profuse diarrhoea, (2) starts to vomit, (3) becomes very thirsty, (4) is eating or drinking poorly, (5) develops a fever, (6) has blood in the stool, or (7) does not get better within 3d.

Management of dehydration in severe acute malnutrition

Determining of the degree of dehydration in children with SAM is difficult: sunken eyes and ↓ skin turgor may be present in severe wasting regardless of dehydration; oedema in kwashiorkor may conceal signs of hypovolaemia.

- Children presenting SAM and diarrhoea should generally receive inpatient monitoring and care.
- All children with SAM and diarrhoea should be assumed to have some dehydration and receive cautious oral/NG rehydration:
  - ReSoMal is a modified ORS that contains less Na^+ and more K^+, and is designed for rehydration of children with SAM.

- Give 10mL/kg/h for the first 2h—orally or via NGT. Monitor at least every 30mins. Then give 5–10mL/kg/h over next 4–10h. Aim for 70–100mL total rehydration fluids over 12h.
- Be alert to development of any features of volume overload and pause ReSoMal if they develop. Reassess in 1h.
- Continue breastfeeding during rehydration. Start F75 as soon as possible and prior to full rehydration depending on clinical condition.
- Prevent development of dehydration by giving 50–100mL ReSoMal with each loose stool.
- ReSoMal may → hyponatraemia: do not use in outpatient settings, and use ORS in preference if profuse watery stools are present.

- IV rehydration may be dangerous in SAM and should be reserved for those with features of shock.
- All children with SAM receiving inpatient care should receive parenteral antibiotics.

Acute diarrhoea: problems and complications

- *Failure to correct dehydration on ORS*:
  - Often due to inadequate provision resulting from vomiting, fatigue, lethargy, or lack of supervision. Reassess, consider need for NG/IV rehydration. There is insufficient evidence to recommend antiemetics in resource-poor settings, and they can → complications.
  - Consider cholera (➲ p. 253) if unable to keep up with profuse stool loss (>15mL/kg/h): may require NG/IV rehydration. Considering Ringer's lactate 75mL/kg IV over 4h (similar to WHO treatment plan C).
- *Worsening diarrhoea on ORS*:
  - Transient intolerance to monosaccharides including glucose in ORS can occur → ↑ stool output on ORS that settles when nil by mouth. Usually improves within a few days. Treat by temporarily restricting ORS and giving IV fluids.
- *Developing abdominal distension on ORS*:
  - Suggests paralytic ileus; may be caused by opiates (e.g. codeine, loperamide) or electrolyte disturbance (esp. hypokalaemia). Manage with IV fluids, ideally containing potassium. Check electrolytes if possible.
- *Failure to correct dehydration with IV rehydration*:
  - Children requiring IV rehydration are very unwell. Examine carefully to rule out other causes of critical illness (e.g. sepsis, pneumonia, malaria).
  - Failure to improve dehydration after WHO treatment plan C is unusual. Consider cholera, esp. if there is profuse diarrhoea. Check electrolytes (including chloride) prior to recommencing IV rehydration.
- *Clinical deterioration during IV rehydration*:
  - WHO treatment plan C involves large volume of fluid. Monitor for fluid overload +/− heart failure (look for respiratory distress, tachycardia, hepatomegaly).
  - Metabolic acidosis may result from GI bicarbonate loss, plus large amounts of chloride in IV fluids. Switch from saline to Ringer's lactate if possible. ↓ K^+ may worsen if IV bicarbonate is required.

- *Seizures*:
  - May result from hypoglycaemia, or hypo/hypernatraemia. Consider sepsis, meningitis, malaria, etc.
  - Shigella can → encephalopathy with seizures—test stool if possible.
- *Ongoing bloody diarrhoea despite antibiotics*:
  - If no improvement after 2d of antibiotics, consider referral to hospital (esp. if dehydrated, younger than 1yr, or had measles recently).
  - Change antimicrobial (e.g. to ceftriaxone or azithromycin) to cover possibility of resistant *Shigella*.
  - If no improvement within 2d after switching to a second antibiotic refer to hospital; consider treating for amoebiasis.

Box 6.7 Oral rehydration solution

ORS is made up with the following ingredients:

- Sodium chloride: 2.6g/L.
- Glucose (anhydrous): 13.5g/L.
- Potassium chloride: 1.5g/L.
- Trisodium citrate, dehydrate: 2.9g/L.

It provides:

- Na^+: 75mmol/L.
- Cl^-: 65mmol/L.
- Glucose: 75mmol/L.
- K^+: 20mmol/L.
- Citrate: 10mmol/L.
- Total osmolarity: 245mmol/L.

- ORS is available in powdered sachets; dissolve in 1L of clean (e.g. boiled/chlorinated) water.
- The ORS composition as shown is sometimes referred to as 'low-osmolarity ORS', replacing a different compositional standard that was abandoned years ago. Use ORS solution within 24h, thereafter discard and prepare a fresh solution.
- Rice-based ORS may be available: it is more expensive than standard ORS but is better in the treatment of cholera.

Persistent diarrhoea

Diarrhoea lasting for >14d is → significant mortality in children, esp. if associated with malnutrition, poor water, sanitation, and hygiene, and poverty. The cause is often multifactorial involving repeated or ongoing infection → small intestinal villous injury, malabsorption (esp. post-infectious lactase deficiency), and micronutrient deficiency. Changes in normal intestinal flora may play a role. There are often several potential pathogens identifiable in the stool, and determining which (if any) are contributing to symptoms can be difficult. Promptly identifying treatable causes and providing good nutrition often → recovery.

Differential diagnosis

1. Serial bouts of acute diarrhoea from different pathogens.
2. Prolonged infection. Common causes (OI: usually opportunistic pathogen in immunosuppressed patients):
   a. Common protozoa:
      i. *Cryptosporidium* spp.
      ii. *Giardia lamblia*.
      iii. *Cyclospora cayetanensis* (OI).
      iv. *Cystoisospora belli*.
      v. *Entamoeba histolytica*.
      vi. *Dientamoeba fragilis*.
   b. Other parasites:
      i. *Strongyloides stercoralis*.
      ii. Blastocystis spp.
      iii. *Fasciolopsis buski* (intestinal fluke).
      iv. *Schistosoma mansoni*.
      v. *Microsporidia* spp. (OI).
   c. Bacteria:
      i. Enteropathogenic *E. coli* (EPEC).
      ii. Enteroaggregative *E. coli* (EAEC).
      iii. *Shigella* spp.
      iv. *Campylobacter* spp.
      v. Non-typhoidal *Salmonella* (NTS).
      vi. *Vibrio parahaemolyticus* (OI).
      vii. *Yersinia enterocolitica*.
      viii. *Clostridium difficile*.
      ix. *Arcobacter butzleri*.
      x. *Aeromonas* spp.
      xi. Ileocaecal TB.
   d. Viruses:
      i. Rotavirus.
      ii. Norovirus.
      iii. Sapovirus.
      iv. Astrovirus.
      v. CMV (OI).
      vi. HIV enteropathy.

3. Small intestinal bacterial overgrowth.
4. Post-infective malabsorption due to 2° hypolactasia.
5. Antibiotic-associated diarrhoea.
6. Micronutrient deficiency esp. zinc, vitamin A.
7. GI lymphoma (esp. with HIV).
8. Acute and chronic liver disease.
9. Chronic pancreatitis.
10. Inflammatory bowel disease and coeliac disease.
11. Congenital syndromic diarrhoea (many genetic aetiologies).
12. Irritable bowel syndrome.

Clinical approach

- Screen for SAM.
- Look carefully for other infections and treat appropriately.
- Consider need for admission to hospital, esp. if systemic infection, dehydrated, or very young.
- Treat and/or prevent dehydration.
- According to treatment plans A, B, or C as appropriate.
- Test for, and treat specific infections:
  - Perform stool microscopy, culture, and sensitivity, and microscopy for ova, cysts, and parasites, if possible. See Colour Plates 5–8.
  - Persistent diarrhoea with blood should be managed with oral antimicrobials effective against *Shigella* spp. Consider treating for amoebiasis if there is no improvement after treatment with two antibiotics for at least 2d each.
  - Giardiasis: *Giardia lamblia* is frequently detected in stool but is not usually pathogenic. However, if *Giardia* is present during ongoing diarrhoea it is sensible to treat, e.g. with oral metronidazole or tinidazole.
  - *C. difficile*: consider if bloody diarrhoea following antibiotics.
- Give appropriate nutrition depending on age and location (Box 6.8).
- Provide vitamin/mineral supplement daily for 14d.
- Choose a preparation based on local availability. Aim to provide at least 2× the recommended daily allowance of folate, vitamin A, zinc, magnesium, and copper.
- Monitor response to treatment:
  - Review children managed as outpatients at least weekly.
  - Children managed in hospital should have daily measurement of temperature, weight, intake, and stool output.
  - Expect >90% to improve within 1wk on low-lactose or lactose-free diet (Box 6.9). If not, look again for infectious causes; consider treatment for small intestinal bacterial overgrowth.
  - Further dietary modification is challenging and depends on context and availability, e.g. minced chicken-based diets, cooked green banana, or elemental feeds. Specialist input is recommended.

Box 6.8 Nutritional management of persistent diarrhoea

Outpatients

- Continue breastfeeding. Encourage exclusive breastfeeding if <6mths.
- Yoghurt contains less lactose than milk; if available, provide yoghurt in place of any animal milk usually taken by the child; otherwise limit animal milk to 50mL/kg/d.
- Ensure nutritious energy-rich diet providing >110kcal/kg/d as small, frequent meals.

Inpatients

- Continue breastfeeding. Encourage exclusive breastfeeding if <6mths.
- Provide a low-lactose diet:
  - If <6mths, not exclusively breastfeeding, and requiring additional nutrition, consider low-lactose infant formula (or yoghurt if appropriate).
  - For children ≥6mths aim to provide 70kcal/100g with 10% calories as protein and <3.7g lactose/kg bodyweight/d:
    - *Example*—full-fat milk: 11g dried or 85mL liquid.
    - Rice: 15g (when uncooked).
    - Vegetable oil: 3.5g.
    - Cane sugar: 3.0g.
    - Water: make up to 200mL.
    - 130mL/kg provides 110kcal/kg.
- If no response to low-lactose diet within 2d, provide a *lactose-free diet with reduced starch* (Box 6.9):
  - If <6mths and not weaned/weanable, use lactose-free (e.g. soy-based) infant formula.
  - For children ≥6mths use egg/cereal protein sources:
    - *Example*—whole egg: 64g.
    - Rice: 3g (when uncooked).
    - Vegetable oil: 4.0g.
    - Glucose powder: 3.0g.
    - Water: make up to 200mL.
    - 145mL/kg provides 110kcal/kg.

- Discharge when improving:
  - Children should have demonstrated sustained ↑ weight and ↓ stool output.
  - Try to normalize diet prior to discharge for inpatients to ensure no rebound effect.
  - Ensure provision of >110kcal/kg/d during recovery.
  - Restriction of milk intake for 7d may be necessary while the small intestinal mucosa recovers.

Box 6.9 Lactose intolerance

Lactase in the brush border of the small intestine hydrolyses lactose (the main carbohydrate in milk) into glucose and galactose. Infants have high concentrations of lactase but in most individuals the concentration naturally declines following weaning. Low lactase → lactose intolerance: incompletely hydrolysed lactose reaches the colon → osmotic diarrhoea, abdominal pain, distension, and flatulence. Some populations (especially in non-tropical countries) persistently express lactase into adulthood. Short-term 2° lactose intolerance may arise at any age when there has been injury to the small intestinal brush border, e.g. as a result of infection or inflammation.

Formal diagnosis of lactose intolerance is difficult; reducing substances in the stool and a low stool pH following lactose challenge are strongly suggestive. Symptoms may be controlled by allowing only small amounts of lactose at a time; slowing gastric emptying, e.g. by mixing milk with cereals; ↓ lactose by fermentation, e.g. yogurt; or taking lactase supplements with milk drinks. Total exclusion of milk to avoid lactose should be avoided in infants and in populations that rely heavily on milk products in the diet.

Diarrhoeal pathogens

Shigella

Causes both endemic and epidemic diarrhoeal disease with children most frequently affected. Shigella infection is also common among MSM where it is often associated with antibiotic resistance. Humans are the only natural host. Transmission is usually direct person-to-person contact (faeco-oral) with a very low infectious inoculum.

- *Shigella flexneri*: main species causing endemic diarrhoea in LMIC.
- *S. sonneii*: second most common species in LMIC, main cause in high-income countries.
- *S. dysenteriae*: generally a rare cause but serotype 1 has been responsible for several major pandemics with high attack rate and severe disease in all age groups. Produces Shiga toxin, associated with haemolytic uraemic syndrome (HUS).
- *S. boydii* is another rare cause.

Clinical features

Highly variable: *Shigella* is commonest cause of acute bloody diarrhoea in children but also a leading cause of watery diarrhoea. Incubation period is usually 1–4d (up to 8d). First manifestations are fever (>70%), headache, malaise, and vomiting. Watery diarrhoea develops a few hours later, followed (in some cases) by abdominal cramps, tenesmus, and passage of frequent small stools with blood and mucus. Very high stooling frequency (>20 times/d) is characteristic.

Intestinal complications Toxic megacolon, rectal prolapse, intestinal perforation, and protein-losing enteropathy. Important cause of persistent diarrhoea.

Extraintestinal complications Dehydration, hypoglycaemia, hyponatraemia, seizures (5–30% of children hospitalized with shigellosis), encephalopathy, invasive infection (e.g. sepsis, meningitis, osteomyelitis), vaginitis.

Post-infectious complications HUS, thrombotic thrombocytopenic purpura (TTP), reactive arthritis, irritable bowel syndrome.

Diagnosis

Gold standard is stool culture. Particularly important to test when resistance profiling may be needed (e.g. travellers, MSM). See Box 6.10.

Management

Described on ➲ p. 234. Supportive care is key. First-line antimicrobial (for adults and children) is ciprofloxacin orally, or ceftriaxone IV if very ill. Alternatives: azithromycin, cefixime, trimethoprim–sulfamethoxazole. Change agent if no improvement in 48h. Consider amoebiasis if no improvement after two antibiotic trials.

Prevention

Clean water, food, and hand hygiene. Several vaccine candidates are in clinical trials.

Non-typhoidal *Salmonella*

Salmonella enterica subspecies *enterica* comprises >2500 serovars. Some of these serovars cause invasive infection in humans (e.g. *S. typhi* and *S. paratyphi*; ➲ p. 17). Others are associated with diarrhoeal disease and

infect animals as well as humans (e.g. *S. enteritidis* and *S. typhimurium*). These are sometimes referred to as non-typhoidal salmonellae (NTS), although they have also have variable propensity to invasion and are common causes of bacteraemia in resource-limited settings (esp. sub-Saharan Africa).

Transmission is often by ingestion of contaminated food but person-to-person spread is possible in areas of high endemicity. Incubation period is 24–48h (up to 72h); bacteria are then excreted in the faeces for up to 8wks following infection.

Clinical features

Range in severity according to the serotype involved. Two (often overlapping) clinical syndromes are seen:

Box 6.10 Diarrhoeal differentials

Infective causes of diarrhoea WITH blood

- *Shigella*.
- Non-typhoidal *Salmonella* (NTS).
- *Campylobacter*.
- Enterohaemorrhagic *E. coli* (EHEC).
- Enteroinvasive *E. coli* (EIEC).
- *Entamoeba histolytica*.
- *Yersinia enterocolitica*.
- *Balantidium coli*.
- *Clostridium difficile*.
- *Vibrio parahaemolyticus*.
- *Aeromonas* spp.
- Whipworm (*Trichuris trichiura*) (➔ p. 272).
- Schistosomiasis.
- *Cystoisospora belli*.
- *Cytomegalovirus*.

Infective causes of diarrhoea WITHOUT blood

- Systemic infections, e.g. malaria, sepsis.
- Rotavirus.
- Astrovirus.
- Enteric adenovirus.
- Noroviruses.
- Sapovirus.
- Enterotoxigenic *E. coli* (ETEC).
- Enteropathogenic *E. coli* (EPEC).
- Enteroaggregative *E. coli* (EAEC).
- Early/mild *Shigella*, NTS or *Campylobacter*.
- Enterotoxin-producing strains of *Staph. aureus*.
- *Cholera*.
- *Clostridia* spp.
- Cryptosporidiosis.
- Giardiasis.
- *Cyclospora cayetanensis*.
- *Strongyloidiasis stercoralis*.
- Food toxins.
- Whipple's disease.

- *Acute enterocolitis*: nausea and vomiting, headache, fever, and malaise, rapidly progressing to diarrhoea with cramping abdominal pains. Initially voluminous and watery, stool changes to bloody with mucus as disease progresses. May be left iliac fossa pain and tenderness. Occasionally ileal involvement is dominant, resembling appendicitis. Toxic megacolon may complicate severe colitis.
- *Invasive salmonellosis*: common in much of sub-Saharan Africa, where predisposing factors are HIV, malaria (esp. malarial anaemia), malnutrition, sickle cell disease, and schistosomiasis (in children). Presents as a severe febrile illness with variable and non-specific clinical features, often no apparent focus. Splenomegaly and hepatosplenomegaly are common. A high index of suspicion is important since bacteraemia may occur alongside pneumonia (e.g. due to other pathogens) and malaria. There may be spread to CSF (esp. young children) and other distal sites.

Diagnosis

Depends on isolation of the bacteria from faecal or blood cultures; sensitivity testing is essential.

Management

While antibiotics are not usually needed in uncomplicated diarrhoeal infection, they will usually be given empirically for bloody diarrhoea. Systemic infection requires IV antibiotics (e.g. cefotaxime/ceftriaxone). Because antimicrobial resistance is common, the choice of agent should be influenced by local sensitivities. HIV-infected individuals should receive antibiotics (e.g. ciprofloxacin). Recrudescence is common in HIV, so 7–14d of antibiotics are often given (up to 6wks if severely immunosuppressed). This should be balanced against the risk of ciprofloxacin driving TB quinolone resistance if coinfection is possible (often will be in patients with advanced HIV disease). Prompt and effective treatment of comorbidities is critical, and if not on ART, a decision must be made about the safest time to start ART.

Campylobacter

Widely endemic and an important cause of acute bloody diarrhoea, *C. jejuni* (also *C. coli*) can also cause food-borne outbreaks. Wild and farmed birds are the major reservoir. Transmission is commonly via contamination of food and water with poultry excreta.

Clinical features

Clinically indistinguishable from *Shigella* infection, and usually self-limiting. Incubation period is 1–3d. Abdominal pain may be prominent even after diarrhoea settles.

Extraintestinal complications Severe, disseminated infection can occur in presence of malnutrition, liver disease, malignancy, diabetes, renal failure, and immunosuppression. Bacteraemia can → infection in distal sites, e.g. meningitis, endocarditis, myocarditis, abscesses. Post-infectious sequelae incl. GBS and reactive arthritis.

Diagnosis

Selective culture is insensitive; PCR and enzyme immunoassay (EIA) assays exist.

Management

Syndromic management of acute bloody diarrhoea is described on ➲ p. 244.

Prevention

Depends on breaking the chain of food and water contamination. No vaccine currently available.

Yersinia

Yersinia infection occurs in cool climates and is a rare cause of diarrhoea in most resource-limited settings. Presents with low-grade fever, bloody diarrhoea, and right-sided abdominal pain resembling appendicitis. More common in young children. Diagnosis is via culture from stool or other sites of infection. Usually self-limiting.

Complications Distal spread is possible, and complications incl. sepsis, peritonitis, and abscesses. Complications are more common in immunocompromised patients or those who are iron overloaded (e.g. haemochromatosis).

Enteric pathogenic *Escherichia coli*

E. coli are a large and diverse bacterial species. Enteric pathogenic strains can be categorized into five main pathotypes as shown. Identification of the various pathotypes is not available outside research or epidemiological surveillance settings, with the exception of EHEC. Management is syndromic and supportive. While antibiotics are provided as part of the syndromic management of bloody diarrhoea in children, they are specifically contraindicated in EHEC infection. No vaccines are currently available.

EHEC (enterohaemorrhagic E. coli)

- Moderately invasive. Produce Shiga toxin (Shigatoxigenic *E. coli*, STEC) or Shiga-like toxin (verotoxigenic, VTEC), may → HUS (Box 6.11). Best-known strain is O157:H7.
- Associated with outbreaks of inflammatory, haemorrhagic colitis, and HUS (occurs in 10%, with 3–5% case fatality). Infections most frequent in the summer months. Cattle are a major reservoir and contamination of food with animal faeces is the most common cause: likely culprits are ground beef, lamb, and unpasteurized milk, but contaminated fruit, leafy vegetables (including salad) and unpasteurized juices can also be responsible.
- Initially watery diarrhoea and abdominal cramps, blood appearing later. Vomiting and abdominal tenderness are common. Incubation period is 3–8d.
- Diagnosis relies on selective stool culture for *E. coli* O157:H7 (sorbitol–MacConkey agar) with toxin testing (various approaches) to detect non-O157 EHEC.
- Antibiotics are specifically contraindicated as they are associated with ↑ risk of HUS.
- Prevention of infection involves improving animal husbandry and slaughterhouse management to prevent contamination of meat with intestinal content; pasteurize dairy products; cook beef adequately; wash hands frequently with soap incl. after contact with farm animals or meat.

ETEC (enterotoxigenic E. coli)

- Non-invasive. Produce heat-stable (ST) and/or heat-labile (LT) enterotoxins that act on intestinal epithelial cells to stimulate fluid and electrolyte loss into the lumen.
- The major bacterial cause of watery diarrhoea. Transmission by the faeco-oral route mainly via contaminated food, less commonly water.
- Presents with high-output watery diarrhoea with vomiting and abdominal cramps, frequently without fever. Incubation period 1–2d.

EPEC (enteropathogenic E. coli)

- Moderately invasive. Attaches to epithelial cells and effaces microvilli causing significant changes in cellular structure and function → changes in fluid and electrolyte handling that drive secretory diarrhoea along with mucosal inflammation.
- Historically considered an important cause of diarrhoea in children but limited pathogenic potential and asymptomatic carriage is common. Can → outbreaks of diarrhoea with variable clinical features.

EIEC (enteroinvasive E. coli)

- Invasive. Causes a clinical picture identical to *Shigella* spp. due to shared virulence genes.
- Rare cause of diarrhoea.

EAEC (enteroaggregative E. coli)

- Non-invasive. Adhere to intestinal mucosa secreting enterotoxins and cytotoxins and stimulating inflammatory activity.
- Unusual cause of acute diarrhoeal disease in children but frequent subclinical infection may contribute to growth faltering, especially as a co-infection. EAEC have been associated with persistent diarrhoea in adults, especially in the context of HIV.

Amoebic dysentery

Entamoeba histolytica is a protozoan parasite that exists in cystic or trophozoite forms (Colour Plate 6a, 6b). During fulminant infection it is extremely

Box 6.11 Haemolytic uraemic syndrome

- Usually a complication of EHEC and (less commonly) *Shigella* infection; some cases arise sporadically, or following pneumococcal disease.
- Shiga or Shiga-like toxins bind to renal vascular endothelium → bacterial internalization and endothelial apoptosis.
- Characterized by a microangiopathic haemolytic anaemia, thrombocytopenia, renal failure, and CNS involvement. Clinical features overlap with those of TTP in which CNS involvement is more common.
- Rapid development of oliguria, haematuria, hypertension, and confusion 5–10d after onset of bloody diarrhoea raises suspicion of HUS.
- Treatment is supportive, renal replacement therapy may be required. There is significant mortality and long-term renal damage in many survivors.

invasive. Responsible for >55,000 deaths annually, and more significant in adults than children. Risk factors for severe infection incl. pregnancy, extremes of age, and immunosuppression, esp. treatment with corticosteroids.

Transmission

Faeco-oral via contaminated food and water; prevalence is highest where human faeces are used as fertilizer. *E. histolytica* has a simple life cycle: ingested cysts change into trophozoites in the intestine and re-encyst as they travel through the colon. Evacuated cysts remain viable and infective for weeks in cool, damp conditions.

Clinical features

- Related to degree and location of tissue damage by trophozoites. Range from an asymptomatic carrier state to fulminant colitis and invasive extraintestinal disease.
- Intestinal amoebiasis usually has an insidious onset with abdominal discomfort and diarrhoea becoming increasingly bloody and mucoid as severity ↑.
- Recto-sigmoid involvement is frequently associated with tenesmus.
- There may be tenderness over the caecum and transverse and sigmoid colon; if there is a liver abscess (which rarely accompanies dysentery), the liver may be enlarged and tender.
- If steroids are given in error, because the diagnosis is confused with ulcerative colitis, there is often a rapid clinical deterioration with high mortality.

Complications

GI complications include toxic megacolon and bowel perforation. Following repeated infection, an amoebic granuloma (amoeboma) may develop (most frequently at the caecum) where it may be palpable and mistaken for a malignant mass.

Extraintestinal complications occur when invading trophozoites travel to the liver via the portal circulation and establish an amoebic liver abscess (➔ Amoebic liver abscess, p. 308).

Diagnosis

Often difficult and relies on the appearance of aspirated abscess contents, response to metronidazole, and positive amoebic serology identification of *E. histolytica* cysts or trophozoites in the stool (see colour plate 6). Demonstration of cysts does not prove amoebiasis as the cause of symptoms since *E. histolytica* cysts are microscopically identical to common, non-pathogenic *E. dispar* cysts. Incidental carriage of *E. histolytica* itself is also possible.

- Examine at least three stool samples for cysts using concentration and permanent stain techniques, ideally before administration of medications or contrast media (interfere with amoebae recovery).
- A 'hot stool' (specimen container kept warm in a warm water bath and examined if possible within 30min) is required to look for trophozoites. A scraping of a rectal ulcer at proctoscopy has a high yield. Examine a wet mount preparation for motile amoebae. Presence of motile *E. histolytica* trophozoites containing ingested erythrocytes is diagnostic of amoebiasis.

- EIA and molecular techniques have improved sensitivity and specificity for *E. histolytica* compared to microscopy but are not currently widely available.
- *E. histolytica* serology useful in non-endemic areas.

Management

- Metronidazole is effective against the trophozoites, but because it has little effect on the cysts, treatment should be followed by a luminal amoebicide, such as paromomycin or diloxanide.
- For adults give metronidazole 800mg oral tds for 5d, followed by paromomycin 25–35mg/kg/d in three divided doses for 7d (alternative to metronidazole: tinidazole 2g daily for 3d; alternative to paromomycin: diloxanide furoate 500mg oral tds for 10d).
- If there are signs of peritonism, add a broad-spectrum antibiotic.

Prevention

Ensure safe disposal of human faeces; prevent faecal contamination of water supplies. Filtering water with sand or diatomaceous earth is effective. Address personal hygiene, including hand washing.

Balantidium enterocolitis

Balantidium coli is a rare protozoal pathogen of humans, existing in cyst and trophozoite forms; cysts are responsible for faeco-oral transmission. Pigs represent an important animal reservoir. Trophozoites invade intestinal mucosa producing inflammation and ulceration. Clinical features resemble amoebic colitis.

Diagnosis rests upon identification of the trophozoite in the faeces. Management is generally symptomatic. Tetracycline 500mg oral qds for 10d is given for severe disease (alternatives include ampicillin, metronidazole, e.g. in children).

Clostridium difficile

Causes infection following disruption of normal bowel flora by antibiotic therapy. An important cause of hospital-acquired diarrhoea.

Clinical features

Due to production of toxins and vary from asymptomatic to severe colitis with toxic megacolon. Disease severity probably depends on combination of patient comorbidity, and degree of exposure to both antibiotics and *C. difficile* spores. In elderly hospitalized patients or those with significant comorbidity, carries a high mortality. Sigmoidoscopy shows characteristic yellow mucosal plaques (pseudomembranes).

Diagnosis

C. difficile can be cultured if present in stool, but asymptomatic carriage of non-toxin-producing strains (or strains that are not currently producing toxin) is common, esp. in young children. Molecular or EIA tests for toxin genes or the toxins themselves are standard of care where the resources exist.

Management

Metronidazole 800mg oral stat, then 400mg oral tds for 10d. Oral vancomycin 125mg qds for 7–10d is an alternative.

Prevention

Avoid indiscriminate or unnecessarily prolonged use of antibiotics. Hand washing, barrier nursing, and environmental cleaning to eradicate spores are fundamental to preventing transmission in hospitals.

Viral causes of diarrhoea

Viruses are major causes of diarrhoea in children, usually non-bloody, and often associated with fever and vomiting. Diagnosis by PCR in research or surveillance settings is not useful for individual patient care. Managed with supportive care as described previously.

Rotavirus

Historically, rotavirus has been by far the most important cause of gastroenteritis in children. Between 2005 and 2015, rotavirus-attributable under-five mortality ↓ by 44%, partly due to successful rotavirus immunization programmes. The epidemiologic importance of rotavirus in the post-vaccine era remains to be seen. Vaccine efficacy appears to be lower in resource-limited countries, compared to affluent populations. High levels of vaccine coverage have not yet been achieved in the countries likely to benefit most, and rotavirus will likely remain an important pathogen in the future.

Clinically Presents with vomiting (which may occur early), fever, and diarrhoea. Diarrhoea is usually watery and large volume, associated with colicky abdominal pains, ill-defined tenderness, and ↑ bowel sounds.

Enteric adenovirus

Serotypes 40 and 41 commonly → diarrhoea.

Clinically Similar to other viral diarrhoeas.

Norovirus

Human enteric caliciviruses belonging to one of two genogroups (GI and GII) are important viral cause of water- and food-borne diarrhoeal outbreaks in both developing and developed countries. Shellfish and salad are often implicated. They are the most common viral cause of epidemic diarrhoea and vomiting in adults ('winter vomiting disease'). Nosocomial spread is common.

Clinically Vomiting common at onset—may be severe; watery diarrhoea rarely severe, usually lasts 12–24h.

Sapoviruses

Associated with sporadic gastroenteritis in young children.

Astroviruses Single-stranded RNA viruses that occur worldwide and → diarrhoea, mainly in children and the elderly. The illness is similar to rotavirus, although generally milder.

Cryptosporidiosis

The protozoal parasite *Cryptosporidium* (mainly *C. hominis* and *C. parvum*) is one of the most important causes of mild and more severe diarrhoeal illnesses in children. It is also a common opportunistic infection in HIV+ve individuals, and a cause of persistent diarrhoea. Asymptomatic infection has been linked to poor growth in children. Transmission is mainly through contaminated water.

Clinical features

Acute watery diarrhoea, indistinguishable from diarrhoea due to other causes. Abdominal cramping pain is often a feature. In HIV+ve individuals, cryptosporidiosis may be very severe, mimicking cholera, and/or be prolonged.

Diagnosis

Faecal detection of the oocysts (4–6μm diameter red spheres on modified ZN stain—see colour plate 6). Oocysts may also be present in duodenal aspirates, bile secretions, biopsy specimens from affected GI tissue, or respiratory secretions on occasions. ELISA/EIA detection kits are available.

Management

Rehydration and supportive care are the mainstays of treatment. Most infections are self-limiting although they tend to last rather longer than many other acute diarrhoeal illnesses. Nitazoxanide may be used for severe infections, though its effect is weak. It is even less effective in HIV-infected individuals, for whom the most effective treatment is ART.

Giardiasis

Giardia lamblia (also known as *G. intestinalis*, *G. duodenalis*) is the most common human protozoan GI pathogen, having a worldwide distribution. While *Giardia* infection can cause diarrhoea, it appears that most infections in LMICs are not associated with acute symptoms. The impact of chronic giardiasis on growth is uncertain.

Transmission

Giardia cysts can survive for long periods outside the host in suitable environments (e.g. surface water) and are not killed by chlorination. Infection follows ingestion of cysts in faecally contaminated water (from humans or animal hosts) or through direct person-to-person contact.

Clinical features

Persistent watery diarrhoea → steatorrhoea, with nausea, abdominal discomfort, bloating, flatus, sulphurous burping, and ↓ weight is classically recognized among returning travellers to endemic areas, who may experience post-infective IBS as a complication. It remains unclear how prevalent and significant this phenotype is among the indigenous population of such areas. See Fig. 6.4 for mechanisms of steatorrhoea.

Diagnosis

Detection of *Giardia* cysts (and occasionally trophozoites) in faecal samples by light microscopy (see colour plate 6). Examine three separate samples, since cysts are excreted intermittently and diagnostic sensitivity is low. Trophozoites may be detected in biopsies of small intestine mucosa. ELISA tests can detect faecal *Giardia* antigens and stool PCR is highly sensitive. Asymptomatic and mixed infection is so common in LMICs that it is by no means certain (or even likely) that *Giardia* identification in stool indicates that it is causing disease.

Management

If there is persistent diarrhoea, and laboratory-confirmed *Giardia* infection, a trial of treatment is reasonable. Many travellers will receive treatment for giardiasis on purely clinical grounds, because of the simplicity of treatment

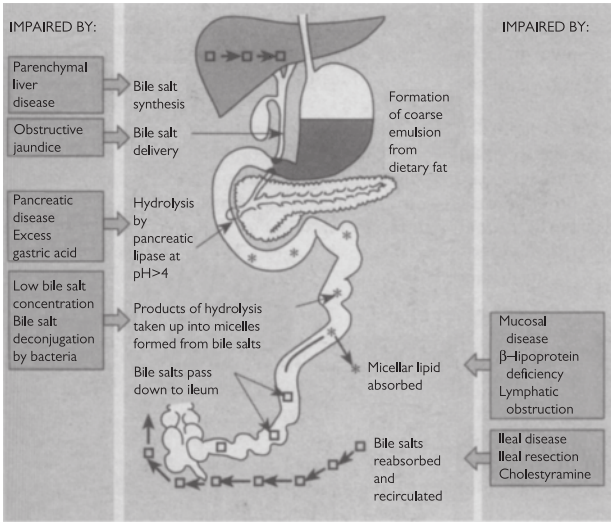


Fig. 6.4 Mechanisms of steatorrhoea.

versus the complexity of investigation. Recommended drugs include metronidazole 2g od oral for 3d, or tinidazole 2g single dose oral.

Cyclospora

Cyclospora cayetanensis is a protozoan coccidian parasite. A rare cause of watery diarrhoea in children, infections may also occur among travellers or in patients with HIV/AIDS. Transmission via contaminated water or food; raspberries, basil, and lettuce have been incriminated. Causes watery diarrhoea that is most severe in non-immune travellers and may be persistent. Mild fever, fatigue, anorexia, and weight loss may occur.

Diagnosis is by finding typical oocysts in faeces which are 7–10μm diameter and contain a 'morula' of eight spherical bodies. The oocysts are also irregularly acid-fast when stained with modified ZN stain.

Treat with co-trimoxazole 960mg oral bd for 7–10d.

Cholera

Vibrio cholerae is the most important cause of dehydrating diarrhoea in adults. Clinical episodes range from asymptomatic infection to acute fulminant watery diarrhoea which, if untreated, may be fatal. Many countries have endemic disease, where individuals build up a degree of protective immunity. 2.9 million cases and 95,000 deaths occur annually in countries with endemic disease, mainly in Africa. Outbreaks and epidemics may occur, esp. when the disease is introduced to a non-immune population, as happened in Haiti in 2010.

Microbiology

Vibrios are Gram −ve, aerobic, comma-shaped bacteria. Most disease has been caused by the O1 serogroup, which is divided into the classical and El Tor biotypes, the latter of which was the main biotype circulating in 2018.

Transmission

V. cholerae is found in brackish water, estuaries, and seawater in association with zooplankton, e.g. cyclops, and shellfish. Under certain conditions of surface water temperature and terrestrial nutrient discharge, plankton will proliferate, → ↑ number of bacteria and setting the scene for transmission. Natural disasters may produce ideal conditions for *V. cholera* outbreaks. Spread is faeco-oral via contaminated food and water. A high infectious inoculum is required, but patients with active disease transmit masses of hyperinfective vibrios, and asymptomatic carriage is extremely common highlighting the need for meticulous hygiene of even asymptomatic individuals to ↓ spread. The bacteria are killed by heating at 55°C for 15mins and by most disinfectants, but can survive in seawater for up to 2wks. The incubation period ranges from a few hours to 5d.

Clinical features

Infection may be asymptomatic; if symptomatic, illness varies from mild, self-limiting diarrhoea to severe, watery 'rice water' diarrhoea of up to 30L/d. Diarrhoea → electrolyte imbalances, metabolic acidosis, prostration, and can cause death from dehydration within hours. Vomiting starts shortly after the onset of diarrhoea in 80% of cases. Shock typically follows around 12h later, with ↓ consciousness due to hypovolaemia and hypoglycaemia. Particularly serious in children who may have a mild fever (adults are afebrile). Renal failure, ileus, and cardiac arrhythmias may precede death; the elderly or those with ↓ gastric acid (e.g. alcoholics) are esp. vulnerable. Muscular and abdominal cramps are common due to loss of Ca^{2+} and Cl^- ions.

Diagnosis

In epidemics, the diagnosis of cholera may be made clinically. In non-epidemic situations, acute watery diarrhoea in adults with severe dehydration or the death of a patient >5yrs suggests the cause is cholera. Dark-field microscopy of faecal material shows comma-shaped bacteria darting about; this is quickly halted upon addition of diluted O1 antisera. Transportation of samples should be in alkaline peptone water; samples should be kept cool. Culture requires selective media such as thiosulfate-citrate-bile salts-sucrose agar (TCBS) agar. EIA rapid tests are available. If possible, specimens should be sent to a reference laboratory for bio- and serotyping. Rapid dipstick tests are available and can provide an early warning that an outbreak of cholera is occurring; however, the sensitivity and specificity of rapid tests are not yet optimal.

Management

Treatment consists mainly of prompt and sufficient rehydration, usually with oral fluids. Cholera cots help to evaluate ongoing fluid losses and help to determine requirements. The most common error is underestimation of volume of ORS or IV fluid required. Details on the management of acute watery diarrhoea are found on ➲ p. 252.

Management particular to cholera includes:

- Provision of antibiotics to cases with severe dehydration as described on ➔ p. 254.
- Use of rice-based ORS when these are available.
- ReSoMal (oral rehydration solution for children with SAM) is contraindicated in patients with profuse diarrhoea due to the risk of hyponatraemia.

Prevention

Public health measures aimed at improving food and water hygiene (Box 6.12), and sanitation are most important. Affordable oral cholera vaccines are available. These are effective in preventing disease in emergency settings and are useful in epidemic control (➔ Immunization, p. 856). Cholera vaccines are also recommended for travellers, esp. healthcare workers, in areas known to have active transmission.

Health education

Essential in preventing outbreaks and limiting the spread of infection during an outbreak. Advice should include food and water hygiene, as well as other

Box 6.12 Treating drinking water

Provision of safe drinking water requires a safe (or treated) water source and a safe storage system. Food hygiene and hand washing are also essential.

- *Boiling*: boiling for 1min and allowing to cool is the most effective sterilization method—boiling kills most microbes even at high altitude.
- *Chlorination*: add 0.5–1.0mg/L sodium hypochlorite solution (e.g. liquid laundry bleach, but check no other ingredients), mix well, and leave for 30mins to kill all bacteria, viruses, and most protozoa; longer exposure in tightly closed container kills *E. histolytica* and *Giardia* spp. and ↓ chlorine taste; not effective against cryptosporidia. Works less well (requires more time) when water is turbid: works best if turbid water filtered or sediment left to settle first. Taste may ↓ acceptability.
- *Iodination*: 8mg/L iodine sterilizes most microbes within 10–30mins at 20°C; longer periods for colder water; and up to 8h to ensure complete sterilization. Taste may ↓ acceptability.
- *Sand filtration (0.15–0.3mm particles 0.5m deep, either in a settling tank or a specially designed receptacle)*: removes particulate matter and up to 50% of bacteria, 20% of viruses, and 50% of protozoa (not cryptosporidia). Cotton cloth filters remove up to 50% of bacteria, less effective for viruses and cryptosporidia. All methods remove the copepod vector of dracunculiasis. Helpful as preliminary stage before boiling or chlorination.
- *Ceramic filters*: require 1μm pore size; use a coarser filter first if water turbid to prevent clogging. Relatively expensive. Ideally, boil water first.
- *Sunlight UV-irradiation*: put 0.5–1L water in clean transparent container (e.g. plastic cola bottle), shake vigorously, and expose to sunlight (e.g. on roof of hut) for 6h. UV light kills many bacteria and protozoa, but some viruses resistant; more effective if water gets hot. Only suitable for small volumes.

measures to ↓ transmission such as disinfecting patients' clothing by boiling for 5mins, drying out bedding in the sun, burying stools, etc. In larger health centres, patient excreta may be mixed with disinfectant (e.g. cresol) or acid before disposal in pit latrines. Semi-solid waste should be incinerated. Funerals have been a source of spread and preventive measures should minimize the risk of mourners arriving from uninfected areas, and potential contamination from ritual washing of the dead and funeral feasts. Public health action plans for the critical early stages of a possible outbreak are found at https://www.who.int/health-topics/cholera#tab=tab_1.

Strongyloidiasis

The nematode *Strongyloides stercoralis* commonly infects humans worldwide, particularly in parts of South America and Southeast Asia. It is a serious condition in the immunosuppressed and may → acute, relapsing, or persistent diarrhoea.

Life cycle

Complex (Fig. 6.5), since reproduction can take place in either of two cycles: an external cycle involving free-living worms or an internal cycle. Contamination of skin or buccal mucosa with damp soil or mud containing infectious filariform larvae → penetration of larvae → larvae travel in bloodstream to the lungs where they cross into the alveolar spaces and bronchi. As they are coughed up and swallowed, they travel to the small intestine, where they mature into adults. Eggs produced by the female pass out in the faeces and continue the external cycle.

Autoinfection occurs by infectious filariform larvae reinvading bowel or perianal skin. This can produce indefinite (>40yrs) multiplication within the host, not requiring further infection. The pre-patent period from infection to the appearance of larvae in the stools is >1mth.

Clinical features

- Immune response (positive *Strongyloides* serology, eosinophilia) limits the infection to the small bowel and also the number of adult worms meaning that infection is usually asymptomatic.
- *Skin manifestations*: larval penetration can cause petechial haemorrhages and pruritis at the site of entry (e.g. perianal skin). Characteristic linear, urticarial eruption (larva currens) may be evident as larvae migrate under skin (Colour plate 15). This is normally transient, but may be followed by congestion and oedema. A creeping urticarial rash may occur in pre-sensitized individuals following reinfection.
- *Respiratory*: symptoms similar to bronchopneumonia with consolidation may result from larval invasion of the lungs; accompanied by eosinophilia.
- *Intestinal*: mild diarrhoea with/without mucus is a common symptom, may alternate with constipation. Intensity depends on worm burden. In severe cases, chronic diarrhoea with malabsorption may ensue.

In immunosuppressed (esp. by steroids or transplantation; HIV not classically a risk factor), those co-infected with HTLV-1, malnourished, or debilitated, massive tissue invasion may occur with severe diarrhoea, ileus, hepatomegaly, and multisystem disease due to blood/lymphatic spread ('hyperinfection syndrome'). Granulomas and/or abscesses occur in liver,

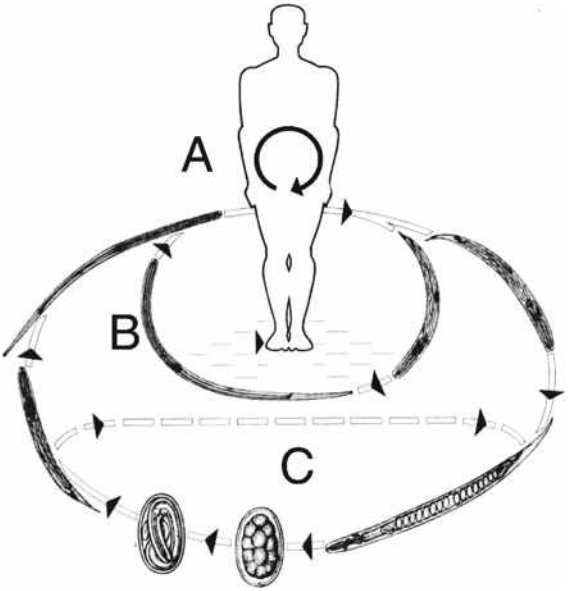


Fig. 6.5 Life cycle of *Strongyloides stercoralis*. The female worms are approx. 2mm in length and live in the small intestine; produce eggs parthenogenetically. In autoinfectious life cycle (A), these hatch within bowel and larvae penetrate intestinal wall to produce more adult worms. Alternatively (B), larvae may be passed in faeces into environmental surface water, and infect new hosts through intact skin (when walking barefoot in puddles). In a third life cycle (C), free-living adult worms give rise to eggs, then larvae, which infect new hosts. Infective larvae are called 'filariform', and those freshly passed in stool are 'rhabtidiform' larvae. Adapted from Piekarski, G, Medical Parasitology in Plates, 1962, with kind permission of Bayer Pharmaceuticals.

kidneys, and lungs, and there may be serous effusions; CNS involvement → pyogenic meningitis and encephalopathy. Eosinophilia is usually absent in hyperinfection. Death usually results from Gram −ve septicaemia.

Diagnosis

Adult worms or rhabditiform larvae may be detected in stool (see Colour Plate 5f), although simple stool microscopy is insensitive. Other methods include modified Baermann technique, agar plate culture, stool ELISA, serology, and stool culture using charcoal. Look for serologic or other evidence of infection in those who are, or are about to be, immunosuppressed (e.g. on steroids).

Management

- Treat all infected patients, not just the symptomatic.
- Give ivermectin 200 micrograms/kg oral od for 2d. Ivermectin does not kill adult worms therefore repeat treatment may be required.
- *Less effective alternatives*: albendazole 400mg po bd for 7d; thiabendazole 25mg/kg po bd for 2d, or 5d in disseminated infection.

Prevention
Requires improving hygiene, encouraging footwear, and education on a community level, as well as monitoring and evaluation.

Whipple's disease

Rare condition caused by the bacterium *Tropheryma whipplei*. Classically, there is ↓ weight, diarrhoea, and malabsorption, but clinical features are varied and often non-specific. Other features incl. fever, lymphadenopathy, arthralgia (e.g. transient or migratory), uveitis, culture –ve endocarditis, coronary arteritis, myocarditis, and encephalopathy. A histopathological diagnosis may be made incidentally on intestinal biopsy showing granulomatous inflammation and periodic acid–Schiff (PAS) staining deposits. PCR for the presence of *T. whipplei* in affected tissues confirms the diagnosis. Treated with 2wks of ceftriaxone 2g od IV, then oral co-trimoxazole (alternatives: tetracycline or minocycline) for 1yr.

Travellers' diarrhoea

Travellers' diarrhoea affects 20–50% of travellers to the tropics/subtropics annually, esp. those from resource-rich regions, young children, backpackers, campers, adventure tourists, and those staying in low-cost accommodation or cruise ships. Most episodes are short-lived and mild. Longer-term consequences incl. chronic or persistent diarrhoea (1–3%), irritable bowel syndrome (3–10%), and GBS (rare). The most common causes are:

- Enterotoxigenic *E. coli*: 30–40%.
- Enteroaggregative *E. coli*: 15–40%.
- *Campylobacter jejuni*: <20%.
- *Shigella* spp.: 5–15%.
- *Salmonella* spp.: 2–5%.
- *Giardia intestinalis*: 3–10%.

Management

- Most episodes are self-limiting.
- ↑ fluid intake. Eat as normally as possible, include, e.g. broth with noodles or salty crackers with sweetened drinks to provide a balance of carbohydrate and salt.
- ORS if diarrhoea frequent or severe, or if there are signs of dehydration, weakness, or muscle cramps.
- Drinks designed for rehydration during sports activities, fizzy drinks and fruit juices do not contain the correct balance of salts for treatment. High osmolarity and sugar content can → ↑ diarrhoea.
- Loperamide (4mg oral once followed by 2mg after each loose stool) shortens the episode in older children and adults with frequent small volume stools. (Do not use loperamide in infants, nor if fever, blood in stools, tenesmus, or severe abdominal pain.)
- Promptly administered short courses of antibiotics ↓ symptom duration (by approx.. 1½d). Ciprofloxacin (500mg bd oral for 3d) would be an appropriate choice for travellers to Africa and South/Central America; azithromycin (1g single dose or 500mg od for 3d) or rifaximin for South/South-East Asia.
- Bear in mind possible impacts on other regular mediations' effectiveness (e.g. antiepileptics, oral contraceptive).

Prevention

Avoid unpeeled fruit and uncooked vegetables, sauces that are not freshly prepared, and food prepared and handled in unhygienic conditions (e.g. by street vendors). Where there is no reliable source of chlorinated water, sterilize water by boiling or with chlorine tablets, or drink bottled water from a reputable source. Outsides of bottled water may be contaminated if bottle has been immersed in water or ice to keep cool. Ice or ice cream may be made using contaminated water. When trekking or in isolated places, it is advisable to carry packets of ORS and a course of antibiotics. Hand sanitizers are useful when handwashing is impossible.

Food poisoning

Food poisoning refers to GI symptoms occurring within a few hours of ingesting food containing a toxin. Microbial infections usually have a longer incubation period as the pathogen proliferates in the intestine (Table 6.1).

Table 6.1 Food poisoning from bacteria or their toxins

Organism/toxin	Principal foods	Time after food	Clinical features
Staph. *aureus*	Meat, poultry, dairy produce, prepared foods	1–6h	D, V, AP
Bacillus cereus	Fried rice, sauces, vegetables	1–12h	V, D, AP
Red bean toxin		1–6h	D, V
Scombrotoxin	Fish (especially dark fleshed)	1–6h	D, flushing, sweating, mouth pain
Mushroom toxin		1–6h	D, V, AP
Ciguatera	Fish	1–6h	Fits, coma, renal/liver failure
Salmonella spp.	Meat, poultry, eggs, dairy produce	8–72h	D, V, AP, fever
Campylobacter spp.	Poultry, raw milk, eggs	2–5d	D, AP
Clostridium perfringens	Cooked meat	6–24h	D, AP, V
Vibrio parahaemolyticus	Seafood	4–96h (mean 12h)	D, V, AP, cramp, headache
Shigella spp.	Faecal contamination	1–3d	D, V, fever
Clostridium botulinum	Poorly canned food, smoked meats	12–36h	Diplopia, paralysis
Listeria monocytogenes	Dairy produce, vegetables, seafood, processed meat	1–7wks	Febrile illness, septic abortion, sepsis/meningitis especially affecting neonates, immunocompromised persons, pregnant women, and the elderly
E. *coli*	Undercooked beef, contaminated veg (e.g. lettuce), unpasteurized milk/juice	3–4d	D, V, cramps, HUS
Y. *enterocolitica*	Pork and beef	24–36h	Fever, AP, D

AP, abdominal pain; D, diarrhoea; V, vomiting.

Clostridium perfringens

C. perfringens produces two forms of GI disease: simple food poisoning (caused by type A, see Table 6.1) and necrotizing enterocolitis (type C).

Necrotizing enterocolitis (pigbel)

This high-fatality illness has become less common following immunization, but still occurs, particularly in the highlands of Papua New Guinea and also in Uganda, Southeast Asia, and China. It occurs when *C. perfringens* type C is eaten, normally in meat that has been cooked some time previously. It has been associated with infection by *Ascaris lumbricoide*s, and a diet rich in sweet potatoes; both are associated with high levels of heat-stable trypsin inhibitors that inhibit luminal proteases, preventing them inactivating the type C toxin.

Clinical features

Symptoms usually begin 48h following ingestion but may start up to 1wk later. It is classified into four types:

- *Type I (acute toxic)*: presents with fulminant toxaemia and shock. Usually occurs in young children; 85% mortality.
- *Type II (acute surgical)*: presents as mechanical or paralytic ileus, acute bowel necrosis, perforation, or peritonitis; 40% mortality.
- *Type III (subacute surgical)*: presents later, with features similar to type II; 40% mortality.
- *Type IV*: mild diarrhoea only, although may → type III. In types II and III, a thickened segment of bowel is sometimes palpable. Blood and pus are passed with the stool in severe disease.

Diagnosis

Isolation of *C. perfringens* from stool or peritoneal fluid culture. Serological diagnosis is also possible.

Management

Type I and II disease require urgent surgery after resuscitation. Surgery may also be required for type III. Give IV chloramphenicol or benzylpenicillin and *C. perfringens* type C antiserum, where available. Milder cases may require glucose and electrolyte infusions, with IV broad-spectrum antibiotics if signs of extraintestinal spread. Give albendazole or mebendazole for *Ascaris*. Oral food intake should begin after 24h.

Prevention

Immunization with type C toxoid.

Intestinal flukes

Common throughout Asia (particularly Southeast Asia), where prevalence may reach 30% in certain populations. Children more heavily infected and prone to symptoms.

- Fasciolopsiasis: caused by *Fasciolopsis buski*; infection follows ingestion of metacercaria attached to the seed pods of water plants contaminated by human and pig faeces. See Figs. 6.6 and 6.7.
- Echinostomiasis: at least 15 *Echinostoma* species infect humans via the consumption of raw or undercooked freshwater snails, clams, fish, and tadpoles. In NE Thailand, commonly associated with *Opisthorchis* infection.
- Heterophyasis: numerous species of small (2.5mm) *Heterophyes* flukes infect humans following consumption of raw aquatic foods and/or insect larvae.

Clinical features

- Attachment of parasites to intestinal mucosa → inflammation and ulceration.

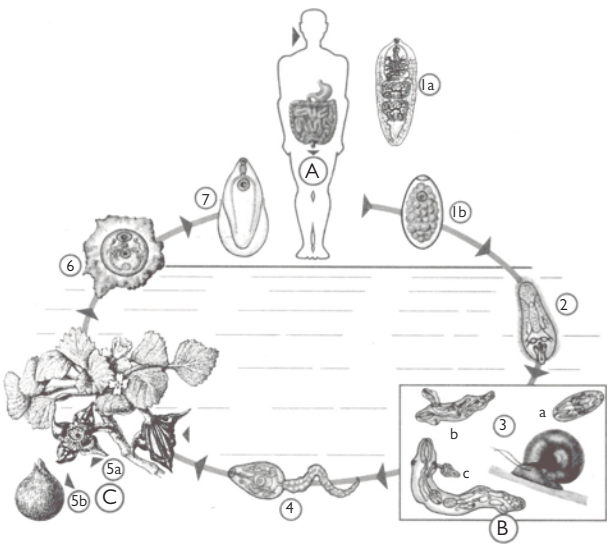


Fig. 6.6 Life cycle of *Fasciolopsis buski*. Adult fluke (1a) lives attached to the intestinal wall. Eggs (1b) are passed in faeces into fresh water, where they release miracidia (2). These invade a suitable snail (B) in which the parasites undergo several developmental stages (3a–c). The cercariae (4) are released into water and encyst as metacercariae on aquatic plants (C). The human or pig hosts become infected by ingesting metacercariae (6), which excyst in the duodenum and attach to the intestinal wall. There they develop into adult flukes (20–75mm × 8–20mm) in ~3mths; adult flukes live ~1yr.

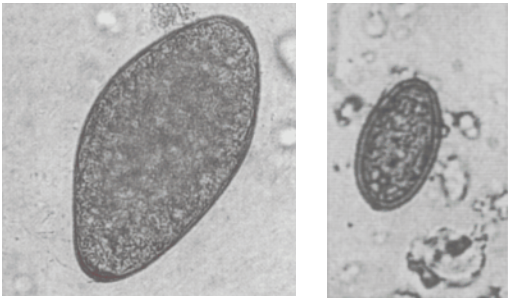


Fig. 6.7 Eggs of *Fasciolopsis buski* (left, 140 × 85μm) and *Heterophyes heterophyes* (right, 25 × 15μm).

- Infections are often asymptomatic; when symptoms occur, they are usually mild and non-specific: diarrhoea, flatulence, mild abdominal pains, vomiting, fever, and anorexia.
- Fasciolopsiasis is occasionally severe → anaemia, malabsorption, oedema, and ascites.
- Eggs (and sometimes adult worms) of *Heterophyes* spp. may enter lymphatics after mucosal penetration and be transported to other sites (e.g. heart, spinal cord, brain, lungs, liver, and spleen) → granulomatous reactions. Myocarditis and neurological deficits may result.

Diagnosis

Faecal examination for eggs after concentration. Differentiation between the various intestinal and hepatic fluke eggs can be difficult. Extraintestinal cases of heterophyiasis are also difficult to diagnose.

Management

- Praziquantel 25mg/kg oral single dose.
- Mebendazole or albendazole may be used for echinostomiasis, although praziquantel is recommended in areas where other trematodes are present, due to its broad efficacy.

Prevention

Concentrate on breaking the faeco-oral cycle (e.g. stopping the use of human and pig excreta as fertilizer) possibly combined with community-based praziquantel treatment and education regarding the consumption of raw/undercooked foodstuffs.

Schistosomiasis (bilharzia)

Common, chronically debilitating, and potentially lethal disease affecting 240 million people worldwide (with 600 million people at risk), causing >200,000 deaths/yr, and second only to malaria in socioeconomic impact from a parasitic disease (Fig. 6.8). Caused by infection with blood flukes (trematodes) *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis*, *S. intercalatum* (all causes of intestinal schistosomiasis), and *S. haematobium* (urogenital schistosomiasis).

Mainly affects poor and rural communities, esp. agricultural and fishing populations. Children are esp. affected.

Life cycle and disease burden

See Fig 6.9. Infection occurs when humans are exposed to (usually stagnant) fresh water infested with the intermediate snail host while swimming, washing, or collecting water. Schistosome cercariae released from the snails penetrate human skin, losing their forked-tail to become schistosomules and enter blood vessels, passing via the lungs to the portal tract, where they mature into adults, pair, and migrate to the vesical plexus (*S. haematobium*) or mesenteric veins (other species). Some schistosomulae continue to circulate in the systemic circulation and are the cause of acute schistosomiasis. The adult worms mate and can produce eggs for several years. Some of the eggs pass into the urinary tract (*S. haematobium*) or into the bowel (other species) before being excreted in urine or faeces. ~50% of eggs do not leave the body, but lodge in bladder or bowel mucosa, or are carried in blood to ectopic sites (e.g. genitalia, lungs, liver, CNS). Disease is caused by the granulomas and scarring around the retained eggs.

Adult worms do not multiply, so level of infection and disease is proportional to the exposure. Usually, there is a slow accumulation of egg granulomas; clinical illness occurs after several years. Infection peaks in early adult life with males/females equally affected. Infections may be very severe in those with regular exposure, e.g. fishermen on African rivers/lakes, rice farmers in Philippines. Prevalence and intensity of infection ↓ in older age groups due to ↓ water contact and ↑ acquired immunity.

Acute schistosomiasis

Acute schistosomiasis is rare in endemic populations and occurs more commonly in travellers in the weeks following exposure. An immunopathological reaction due to hypersensitivity to circulating juvenile schistosomules, immune complex deposition, pro-inflammatory cytokine production, and the toxic effects of eosinophilic proteins. Previously called Katayama fever, originally described as a result of infection with *S. japonicum*, now recognized to occur with *S. mansoni* (commonly) and *S. haematobium* (less commonly).

May be preceded by cercarial dermatitis ('swimmer's itch'), which occurs hours after infection: pruritic papular rash with oedema, erythema, and eosinophilia caused by reaction to cercariae upon skin penetration that resolves spontaneously within 10d.

Clinical features

- Acute schistosomiasis ('Katayama fever') characteristically presents with fever, chills, sweating, fatigue, anorexia, headache, diarrhoea, dry cough, wheeze, hepatosplenomegaly, lymphadenopathy, and urticaria.

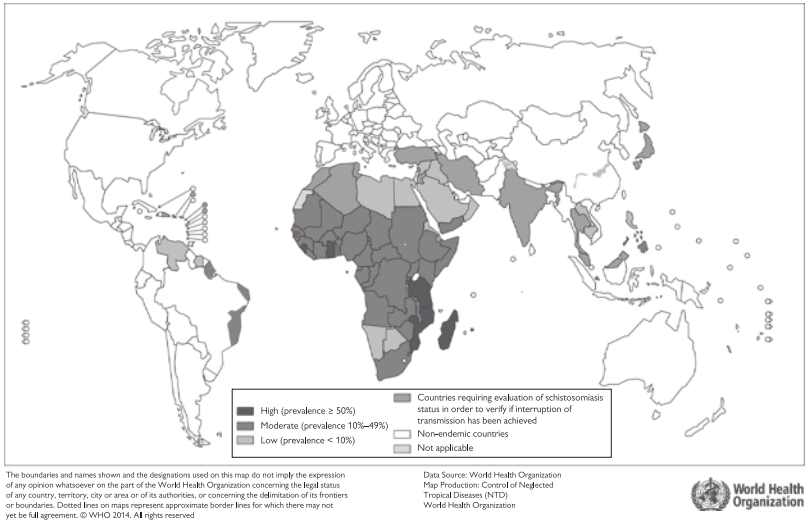


Fig. 6.8 Distribution of schistosomiasis, worldwide, 2012.

Source: Control of Neglected Tropical Diseases, (NTD), World Health Organization © WHO, 2013. All rights reserved.

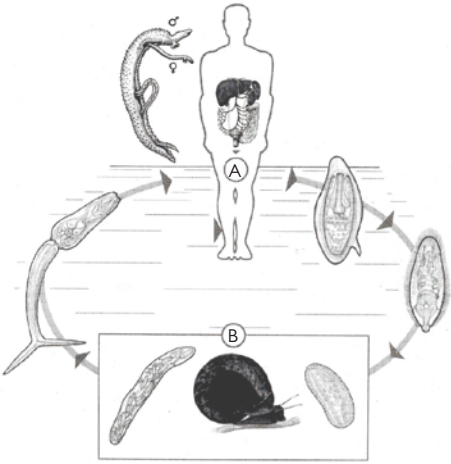


Fig. 6.9 Life cycle of schistosomiasis. Adult worms live in venous plexuses in pelvis; male wraps around female and encloses it in its gynaecophoral canal. Human host (A) sheds ova in stool or urine; these hatch, releasing miracidia, which infect freshwater snail host (B). After further development, cercariae are released into the water, which penetrate skin of humans during water contact. Adapted from Piekarski, G, *Medical Parasitology in Plates*, 1962, with kind permission of Bayer Pharmaceuticals.

- Usually marked eosinophilia and ↑ immunoglobulins. Serial serology shows ↑ titres of anti-schistosomal antibodies, but may be −ve during early acute schistosomiasis. Ova are absent from urine or stool early in the course. Symptoms may persist for weeks, particularly fatigue.

Chronic schistosomiasis

In chronic schistosomiasis, eggs become lodged in capillaries and induce granulomatous inflammation and fibrosis which may affect many organs. Eosinophilia wanes and is not a prominent feature in established schistosomiasis.

Hepatosplenic disease

- Major causes are *S. mansoni* (Africa, Middle East, S America), and *S. japonicum* (E and SE Asia).
- Periportal fibrosis → hepatosplenomegaly (spleen may be massive) and portal hypertension with porto-systemic collateral circulation, ascites, and oesophageal/gastric varices.
- Liver enzymes and albumin are usually normal, without liver failure until very late stages. Hypersplenism → pancytopenia. Characteristic USS appearance (pipe-stem fibrosis around portal veins, scarring of liver surface).
- Other causes of liver cirrhosis may coexist, but in a mixed picture, always treat for schistosomiasis because established periportal fibrosis may improve substantially with treatment.

Intestinal disease

- Same causes and distribution as hepatosplenic disease. Most infections are asymptomatic.
- Eggs reaching the superior and inferior mesenteric venous plexuses (and superior haemorrhoidal veins in *S. japonicum*) may pass through to the intestinal mucosa involving both small and large bowel.
- Chronic colonic inflammation may cause intermittent, bloody diarrhoea with tenesmus, pseudopolyp formation, anaemia/hypoalbuminaemia, and rectal prolapse giving a clinical picture similar to that of ulcerative colitis or proctitis.
- Involvement of the small intestine may cause protein-losing enteropathy or intussusception.
- A 'bilharzioma' is a mass of schistosomal eggs, which may be found in the omentum and/or mesenteric lymph nodes.

Genitourinary disease

- Caused by *S. haematobium* infection. Occurs across Africa and the Middle East.
- Sequelae of infection include bladder fibrosis and calcification with ↓ capacity, and blockage of vesicoureteric orifice → ureteric obstruction, hydroureter, hydronephrosis, reflux, and 2° infection. Patients may have terminal haematuria (visible blood in last few drops of urine) or haemospermia. ↑ risk of squamous cell carcinoma of the bladder at a relatively young age.
- Males with urinary schistosomiasis may experience nuisance symptoms of haemospermia and lumpy semen.
- Female genital schistosomiasis may involve pelvic structures, including the uterus and fallopian tubes. Granulomas on the cervix may resemble cervical cancer on speculum examination, and the surface of the cervix may have a characteristic 'gritty' texture when scarped with a curette. There may be genital lesions, PV bleeding, and dyspareunia. There is an ↑ risk of HIV acquisition and risk of adverse pregnancy and perinatal outcomes.

Other sequelae of chronic infection

- *CNS disease*: rare, but serious complication of ectopic egg deposition. Eggs of *S. japonicum* may embolize to brain → meningoencephalitis or focal epilepsy. *S. mansoni* or *S. haematobium* eggs occasionally embolize to spinal cord, → cauda equina syndrome, transverse myelitis, paraplegia, or bladder dysfunction.
- *Pulmonary disease*: embolizing eggs (especially *S. haematobium*) occasionally occlude the pulmonary capillary bed → pulmonary hypertension with breathlessness, fatigue, syncope, chest pain, and signs of RV failure.
- *Other sites*: very rarely, there may be placental, arthropathic, or cutaneous schistosomiasis.
- *Bacterial superinfection*: bacteria (e.g. *Salmonella* spp.) may colonize adult worms, providing a source for bacteraemic episodes.

Diagnosis

- Always a history of exposure, but may be few clinical signs.
- Diagnosis usually by finding eggs in urine (*S. haematobium*) or faeces/rectal biopsy specimen (other species). See Colour Plate 7.

- Serology is accurate, but cannot distinguish current from past schistosomiasis.
- Urine dipstick for blood is a sensitive screening method for urinary schistosomiasis. Filtration or sedimentation of urine prior to microscopy ↑ yield.
- Thick faecal smears (Kato–Katz preparation) are examined under low (100×) magnification. Live ova have a flickering organelle ('flame cell') seen under high power. Collected eggs may be hatched in freshwater to demonstrate miracidia.
- Depending on the presentation and site of infection, other methods include liver biopsy and further radiological imaging. In biopsies, distinguish dead ova (calcified, partially collapsed, etc.), which persist for years, from viable ova which need treatment.

Management

Permanent cure is feasible in non-endemic areas, but not usually in endemic areas due to high rate of reinfection—unless there is a control programme in place. In cases where treatment does not achieve a full cure, egg production is ↓ by >90%.

Acute schistosomiasis

Drugs are poorly active against schistosomules. Give oral prednisolone to suppress the acute reaction, then praziquantel (dose depending on likely strain as for chronic disease, below). Repeat 3mths after the last risk exposure so as to ensure maturation has occurred into the adult fluke against which praziquantel is active. Viable ova should no longer be excreted 6mths after effective treatment. Antibodies persist lifelong.

Chronic disease

- Praziquantel is effective against all schistosome species. For most species, give two doses of 20mg/kg oral during 1d (three doses of 20mg/kg for *S. japonicum*). If possible, take after food. *S. mekongi* may require repeated doses. For CNS disease, give 35mg/kg ×3 doses during 1d. Paediatric dosage is the same.
- Oxamniquine is a possible alternative for *S. mansoni*.
- Surgical treatment is not recommended. Even chronic/fibrotic lesions will improve, especially in the young, and CNS disease may show resolution even after treatment.

Prevention/control

- Education and improved sanitation.
- Mass treatment of high-risk groups in high endemic areas (school-aged children, women of child-bearing age, certain occupational groups).
- Personal protection, e.g. rubber boots for rice farmers.
- Avoid recreational swimming in at-risk areas.
- Rapid, vigorous drying following contact may kill cercariae that have not fully penetrated skin.
- Molluscicides (costly and have environmental consequences).

Soil-transmitted helminths

Soil-transmitted helminths (STHs) are a group of intestinal parasites transmitted via contamination of soil with human faeces without the need for an intermediate host. As well as sharing the same mode of transmission, approaches to diagnosis and treatment/control are similar. STHs are the nematode roundworm *Ascaris lumbricoides*, whipworm (*Trichuris trichiura*), and hookworm (*Necator americanus* and *Ancylostoma duodenale*). Other STHs *Strongyloides stercoralis* and *Enterobius vermicularis* are sometimes included among STHs and are considered elsewhere (➲ p. 256 and p. 277, respectively). See Fig. 6.10 for the size and appearance of helminth ova; see Colour Plate 5.

For detailed epidemiologic data and an introduction to STH diagnostic techniques see 🖰 http://www.thiswormyworld.org and 🖰 http://www.childrenwithoutworms.org.

Ascariasis

Ascaris lumbricoides infects >800 million people, mainly children and young people living in rural areas, esp. where human faeces is used as a fertilizer.

Lifecycle

See Fig. 6.11. Eggs containing larvae are ingested and hatch in the small intestine. Larvae penetrate the intestinal wall and migrate via bloodstream to the lungs, where they penetrate alveoli and ascend tracheobronchial tree to be swallowed. Returning to the intestine they develop into mature worms, beginning egg production >2mths after ingestion. Adult worms live 10–24mths and female worms lay >200,000 eggs/d. Eggs passed in faeces persist in warm humid soil for years, resistant to cold and detergents.

Clinical features

Most infections are asymptomatic. May cause a variety of clinical problems particular to different stages of its lifecycle. Most morbidity relates to wasting/stunting among children with heavy infection:

- *Larval migration*: 10–14d after infection, larvae transiting the lung may trigger a pulmonary hypersensitivity response (Löeffler's syndrome) with cough, wheeze, eosinophilia, and patchy infiltrates on CXR. The illness is usually mild and self-limiting. Occasionally, ectopic migration to the CNS → irritability, convulsions, meningism. Ocular granulomas, similar to those of *Toxocara canis*, may occur.
- *Adult worms (related to worm burden)*: mild infections usually asymptomatic, but may → ↓ appetite, abdominal discomfort, and dyspepsia. Heavy infections in children may → anaemia and malabsorption of vitamins A and C, proteins, fats, lactose, and iodine, with consequent growth retardation and neurocognitive delay.
- *Adult worms (related to a worm bolus)*: a bolus of adult worms may cause bowel obstruction (usually near the ileocaecal valve), intussusception, volvulus, or perforation. If intestine is perforated, eggs released into peritoneum may cause chronic granulomatous peritonitis.
- *Adult worms (related to ectopic worms)*: Worms may enter common bile duct or pancreatic duct → biliary colic, cholecystitis, pancreatitis, cholangitis, and liver abscess, all +/− 2° bacterial infection. May enter the appendix → appendicitis. High fever or exposure to anaesthetics can cause adult worms to migrate to the stomach, and worms are often vomited up by febrile patients; rarely they come to rest in to ectopic sites (e.g. Eustachian tubes).

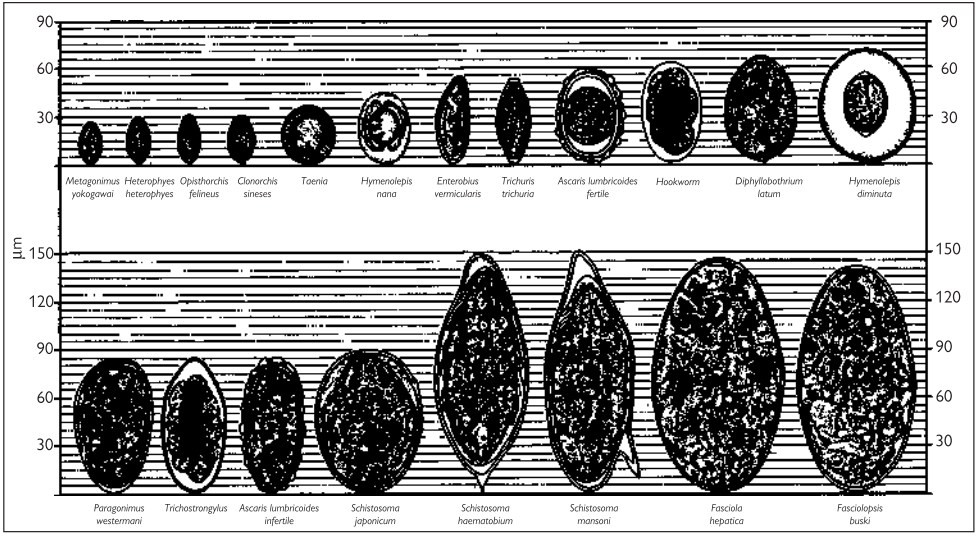


Fig. 6.10 Relative size and appearance of helminth eggs. Reproduced with permission from the WHO from WHO Bench Aids for the Diagnosis of Faecal Parasites.

**Schistosoma mekongi* and *Schistosoma intercalatum* have been omitted. Eggs of *S.mekongi* measure 51–78µm; eggs of *S.intercalatum* measure 120–240µm long.

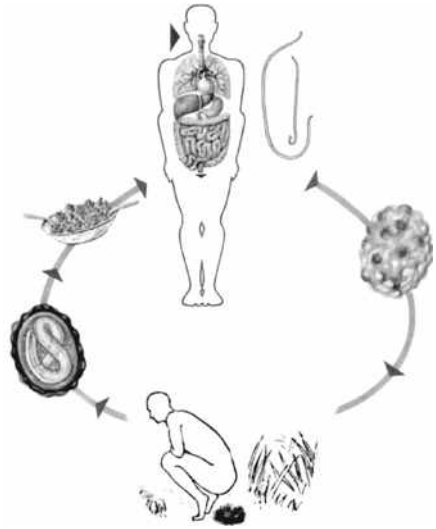


Fig. 6.11 Life cycle of *A. lumbricoides*. Vegetable gardens are faecally contaminated by eggs, which become embryonated (infectious) after 1–7wks in the soil. Ingested eggs hatch in the intestine, larvae migrate through lungs (see text), are then swallowed to become adult worms (females up to 40cm, males smaller). Adapted from Piekarski, G, Medical Parasitology in Plates, 1962, with kind permission of Bayer Pharmaceuticals.

Diagnosis

- Marked eosinophilia occurs during larval migration (differential diagnosis includes toxocariasis, hookworm, strongyloidiasis, schistosomiasis, and tropical pulmonary eosinophilia (➔ Tropical pulmonary eosinophilia, p. 206)).
- Intestinal infection is detected by identifying worms/eggs in faeces.
- Worms may be seen on AXR or barium studies as string-like or tramline shadows.

Management

- Albendazole 400mg oral stat (½ dose if <3yrs) kills adult worms. Alternatives in adults/children >1yr: mebendazole 500mg oral stat or 100mg bd for 3d. Alternative is ivermectin.
- Treat Löeffler's syndrome with prednisolone, followed by albendazole 2–3wks later to kill adult worms.
- Intestinal or biliary obstruction is best managed conservatively (analgesia, NGT, antispasmodics, IV fluids, consider ingestion of oral contrast to help expel the worms) followed by antihelminthic treatment once the acute phase is over.
- Laparotomy may be necessary for worsening/persistent obstruction, appendicitis, or intestinal perforation.

Whipworm

Trichuris trichiura infects >450 million people, esp. children.

Life cycle

See Fig. 6.12. Eggs passed in faeces become infectious in the soil; eggs containing larvae are ingested and hatch in small intestine. Larvae attach to the small intestinal mucosa and develop into mature worms, which tend to live in the caecum and ascending colon. There is no pulmonary migration.

Clinical features

Most infections are asymptomatic. Pathology relates to adult worms burrowing into the intestinal submucosa, which can → abdominal pain and tenderness, with diarrhoea and anaemia. Severe cases may present with trichuris dysentery or rectal prolapse.

Diagnosis

Detection of eggs in faeces. In severe cases colonoscopy may reveal adult worms, and biopsies show an eosinophilic inflammatory infiltrate.

Management

Albendazole 400mg oral od for 3d, or mebendazole 500mg oral od (or 100mg bd) for 3d. Alternative is ivermectin. Efficacy is partial; 3d of albendazole cures >80%, therefore consider follow-up.

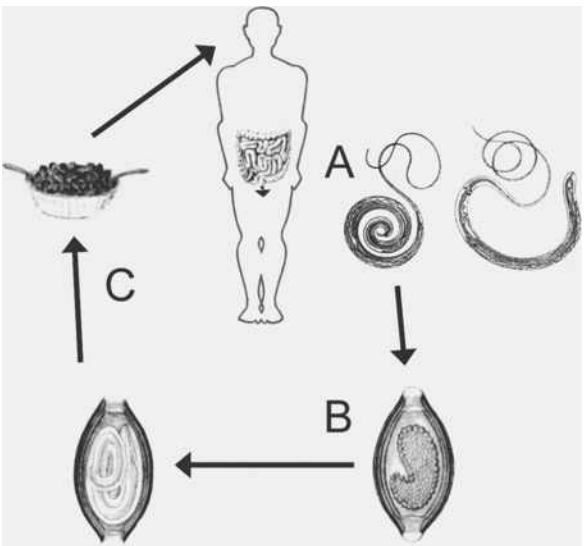


Fig. 6.12 Life cycle of *Trichuris trichiura*. The adult worms (A) are 75cm long (male, shown on the left, is more tightly curled) and live mainly in the large bowel. The eggs (B) are shed in large numbers and become embryonated (infectious form, C) after ~2wks to ~6mths in the environment. They are then ingested, e.g. on food or on fingertips, to become new adult worms.

Hookworm

Infection by *Necator americanus* and *Ancylostoma duodenale* affects >450 million people. Heavy hookworm infections occur among both children and adults.

Life cycle

See Fig. 6.13. Larvae are free-living in the soil, and usually infect via penetration of skin (e.g. bare feet). May remain dormant in connective tissue or muscle or migrate directly in the bloodstream to the lungs, where, like *Ascaris*, they penetrate the alveolae, ascend the bronchial tree to be swallowed, and develop into mature worms in the small intestine. *A. duodenale* can also infect through the oral route.

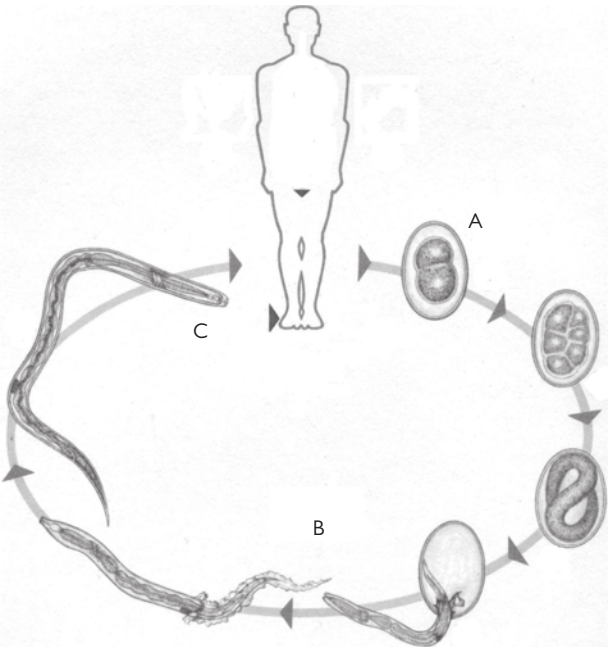


Fig. 6.13 Life cycle of hookworm – best under moist, warm, shady conditions. Eggs are passed in stool (A) and larvae hatch in 1–2d, releasing rhabditiform larvae (B), which, after 5–10d, become infective filariform larvae (C), which can survive 3–4wks in favourable environmental conditions. On contact with human host, infective larvae penetrate skin and are carried through blood vessels to heart and then lungs. They penetrate into pulmonary alveoli, ascend bronchial tree to pharynx, and are swallowed. Larvae reach small intestine, where they mature into adults. Adult worms can survive several years attached to the intestinal wall with resultant blood loss by the host.

Clinical features

- May experience itch at the cutaneous site of infection.
- Most serious effects are anaemia and protein deficiency caused by blood loss at site of intestinal attachment of adult worms. When children are continuously infected by many worms, loss of iron and protein can ↓ growth and neurocognitive development.
- May cause symptoms during pulmonary migration (Löeffler's syndrome).
- Wakana syndrome refers to nausea, vomiting, and pharyngeal discomfort with respiratory symptoms, accompanying per-oral infection.

Diagnosis

Suspect in individuals with microcytic anaemia. Hookworm ova are often abundant in stool.

Management

- Albendazole 400mg od stat or mebendazole 500mg stat (or 100mg bd for 3d).
- Iron supplements and nutritional support may be required.

Public health control of STH

- *Education*: improve hygiene and protect food from dirt.
- *Sanitation*: prevent soil contamination by faeces (e.g. by providing latrines).
- *Mass treatment*: indicated annually when baseline prevalence of infection >20%, twice a year if >50%. Give single-dose albendazole or mebendazole to pre-school (>12mths) and school-age children, women of child-bearing age (including those pregnant in 2nd and 3rd trimesters and breastfeeding where severe anaemia is a severe public health problem). Mebendazole is poorly absorbed and thus preferred for pregnant women. See https://apps.who.int/iris/handle/10665/258983

Toxocariasis

The canine and feline roundworms *Toxocara canis* and *T. cati* have a worldwide distribution. Humans are accidental hosts: adult *Toxocara* worms do not develop in humans, yet larvae migrate around the body and may persist for >10yrs, causing visceral larva migrans and ocular disease.

Life cycle

Eggs excreted in dog or cat faeces become embryonated in soil and are later ingested by humans. Larvae hatch in stomach, penetrate intestinal mucosa and enter circulation via mesenteric blood vessels, from where they may migrate to brain, eye, and other organs.

Clinical features

Depend upon density of infection:

- Visceral larva migrans occurs predominantly in children <5yrs. Typical features are fever, hepatosplenomegaly, cough/bronchospasm, and eosinophilia. CNS involvement (seizures, encephalopathy, and/or neuropsychiatric symptoms), myocarditis, and nephritis have been described. In most cases, the disease resolves spontaneously <2yrs, although it can be fatal, particularly if there is CNS involvement.
- Ocular toxocariasis usually manifests in slightly older children (5–10yrs) and is an important cause of ↓ visual acuity in the tropics. Usually presents with unilateral visual impairment. Peripheral involvement of the retina by subretinal granulomata and choroiditis resembles retinoblastoma in the early stages. Diffuse endophthalmitis or papillitis and 2° glaucoma can occur.
- Co-infection with *Ascaris* and *Trichuris* may also occur. 2° infection with gut bacteria carried by the larvae is common.

Diagnosis

Clinical suspicion; history of exposure, particularly to puppies; fever and organ involvement, eosinophilia, ↑ gamma globulins.

ELISA using recombinant antigens to second-stage larvae has high specificity and reasonable sensitivity. CXR may show mottling in lung disease. Demonstration of larvae is difficult, though they are sometimes present at the centre of granulomatous lesions at biopsy or postmortem.

Management

Albendazole 400mg oral bd for 5d; alternatively, thiabendazole or diethylcarbamazine. Steroids may be required for ocular disease.

Prevention

- Educate pet owners; avoid contamination of soil by dog and cat faeces near houses and child play areas.
- Control stray dogs and cats.
- Regular deworming of cats and dogs beginning at 3wks of age.

Perianal complaints

Perianal itching/discomfort

May be caused by:

- *Skin infection or damage*: e.g. due to enterobiasis, tinea cruris, psoriasis, contact dermatitis, lichen planus, lichen sclerosis, leukoplakia, *Corynebacterium minutissimum* (the causative agent of erythrasma).
- *Surgical conditions*: e.g. haemorrhoids, fissure-in-ano, fistulae, skin-tags, polyps, malignancy.

Passage of worms in stool

May occur 2° to infection with *Ascaris lumbricoides*, *Taenia saginata* and *T. solium*, and *Hymenolepsis nana* (see Fig. 6.12 for sizes of mature worms).

Lower GI bleeding

In young children, usually infective or a surgical cause e.g. intussusception associated with pain or Meckel's diverticulum.

In adults, differential diagnosis incl. haemorrhoids, colonic malignancy, diverticular disease, angiodysplasia, schistosomiasis, and amoebic or bacterial dysentery. Other causes in HIV+ve individuals include TB, disseminated fungal infection (e.g. histoplasmosis), and intestinal KS. Inflammatory bowel disease is rare in the tropics (although ➲ Box 6.6, p. 236). Blood in stool may rarely represent a particularly brisk upper GI bleed.

Unless cause is obvious consider imaging +/− endoscopy and surgical review where available.

Enterobiasis (threadworm, pinworm)

The STH *Enterobius vermicularis* is a common infection of young children worldwide.

Life cycle

See Fig. 6.14. Transmission is usually faeco-oral (pruritus ani → scratching → eggs transferred on fingers or under fingernails from anus to mouth; eggs may also be carried on contaminated bed linen or fomites). Ingested ova hatch in the stomach and larvae migrate to the appendix and caecum where they invade the crypts and mature into adult worms (9–12mm long). Females migrate through anus (usually at night) and burst, depositing eggs on perianal skin and perineum, which are then carried on faeces or picked up under fingernails during scratching. No multiplication inside body. Cycle takes 2–4wks.

Clinical features

Infected individuals are asymptomatic until female deposits her eggs perianally, inducing intense pruritus. General symptoms incl. insomnia, restlessness, ↓ appetite, ↓ weight; children are often irritable and may have enuresis. Worms can enter the vulva, → mucoid discharge and pruritus, may also occasionally be found in ears and nose. 2° bacterial infection of skin damaged by scratching may occur. *Enterobius* worms may be seen in histologic sections of appendicectomy specimens; it is unclear whether these worms are incidental findings or contribute to acute appendicitis.

Diagnosis

Requires detection of eggs on swabs from either perianal region (patient can use Sellotape applied the perianal skin and then to a glass slide, before

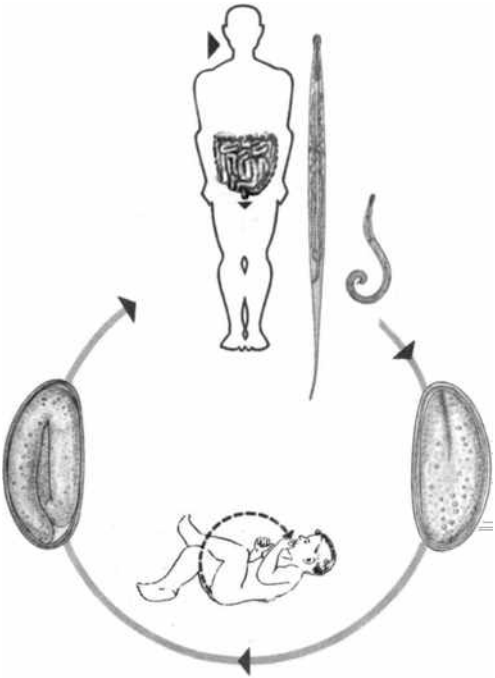


Fig. 6.14 Life cycle of threadworm (*Enterobius vermicularis*). Eggs are ingested (e.g. from fingers which have scratched itchy perianal skin). Larvae hatch in intestine, develop, and penetrate mucosa. Male and female worms mate in intestine and smaller males die; gravid females (about 12mm long) migrate through anus and deposit up to 10 000 eggs on perianal skin. Adapted from Piekarski, G, *Medical Parasitology in Plates*, 1962, with kind permission of Bayer Pharmaceuticals.

bathing), under fingernails, or (less commonly) in faeces. Occasionally, adult worms may be seen around anus at night.

Management

Only beneficial in symptomatic individuals, since reinfection is very common, unless there is change in behaviour. Ideally treat whole family and school members. A single dose of albendazole 400mg oral (children 12–24mths 200mg) or mebendazole 100mg repeated after 2–3wks.

Prevention

- Education to improve personal hygiene.
- Scrub children's hands before meals and after defecation.
- Keep fingernails short.
- Wash bedclothes, underwear, and nightclothes regularly at 55°C for several days after treatment.

Taenia saginata (the beef tapeworm)

See Figs. 6.15 and 6.16. Despite being called 'beef' tapeworm, humans are only definitive hosts of the tapeworm—larval (cyst) form affects bovines. *T. saginata* is common wherever raw beef is eaten, e.g. Ethiopia. Adult worm is typically 3–5m long (some reach 10m) and attaches, via suckers, to upper small intestine wall. Adult worms may shed up to 50,000 eggs/d (contained in proglottids, or sometimes in stool) for >10yrs. Mature proglottids are highly motile and conspicuous in the faeces.

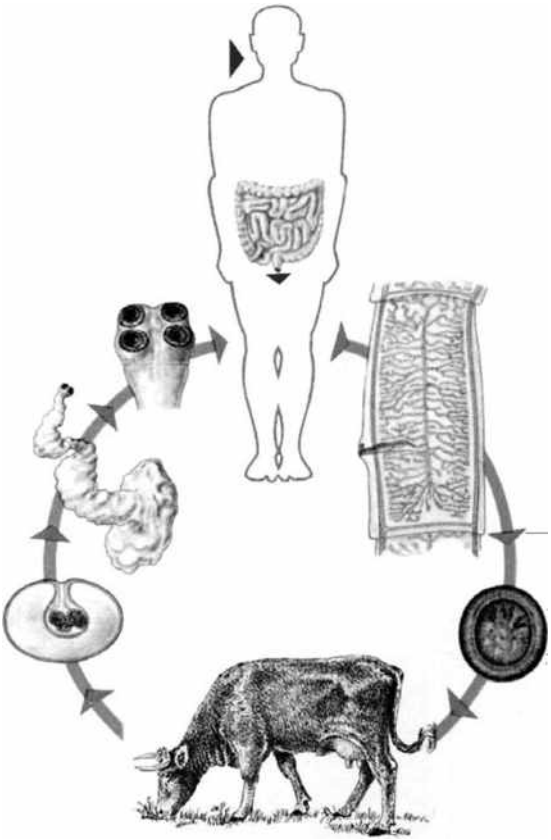


Fig. 6.15 Life cycle of *T. saginata*. Man ingests cysticercus in beef, which evaginates, and scolex attaches to wall of intestine. Adult worm grows to several metres length in intestine, releasing gravid segments (proglottids) and some free eggs. Cattle become infected when grazing on grass contaminated with faeces.

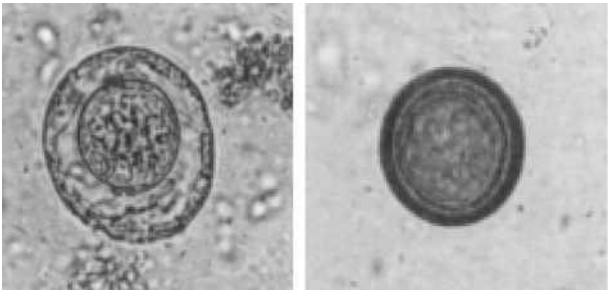


Fig. 6.16 Egg of *H. nana* (30 × 45μm) and of *T. solium* (30 × 45μm diameter).

Patients may have vague abdominal pain, distension, anorexia, and nausea, although infection is often asymptomatic. Occasionally, motile proglottids may be felt emerging from the anus.

Diagnosis

Eggs may be seen on faecal microscopy, but are often absent because they are contained within proglottids. If stool is –ve, ask patient to collect proglottids to show you. Intact proglottids can be speciated according to number of uterine branches.

Management

Praziquantel 10mg/kg oral as a single dose is highly effective; albendazole has some activity.

Prevention

Avoid eating undercooked beef (cysts destroyed >48°C). Improve sanitation. Avoid cattle grazing in areas of open-field defecation.

Taenia solium (the pork tapeworm)

Cysts are eaten in poorly cooked pork (the intermediate host) and mature in the small intestine. The adult tapeworm attaches to the mucosal surface by two encircling rows of hooklets, measuring 2–3m (up to 8m). Unlike *T. saginata*, humans are also readily infected by larval form of tapeworm after ingesting eggs excreted by a human carrier. An alternative route of acquiring cysticercosis is by auto-infection from faeco-oral contamination. Symptoms of adult worm infection are as for *T. saginata*. Proglottids are smaller (712 × 6mm) and less motile. See Neurology chapter for *T. solium* life cycle.

Management

Praziquantel 10mg/kg oral as a single dose is highly effective; albendazole has some activity.

Hymenolepsis nana (the dwarf tapeworm)

H. nana is slender, 3–4cm, and the worm is seldom seen in the stool, but may give rise to abdominal symptoms like other tapeworms. *H. nana* has both larval and adult stages in humans and does not require intermediate hosts. Infection with several hundred worms is common. Since encystation

occurs within small intestinal villi, there is immune stimulation → eosinophilia. Characteristic eggs are seen on faecal microscopy.

Management

Praziquantel 25mg/kg oral as a single dose.

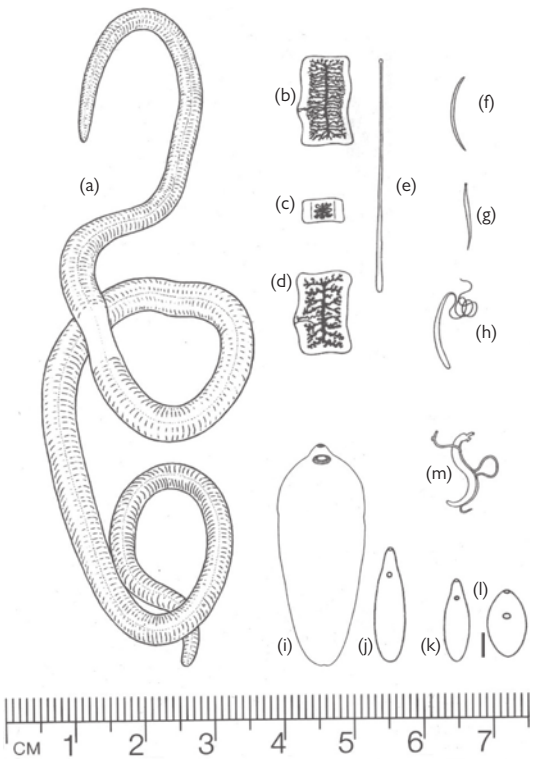


Fig. 6.17 Sizes of mature worms. a = *Ascaris lumbricoides*; b = proglottid of *Taenia saginata*; c = proglottid of *Diphyllobothrium latum*; d = proglottid of *Taenia solium*; e = *Hymenolepis nana*; f = *Ancylostoma duodenale*, *Necator americanus*; g = *Enterobius vermicularis*; h = *Trichuris trichiura*; i = *Fasciola hepatica*; j = *Clonorchis sinensis*; k = *Opisthorchis felineus*, *O. viverrini;* l = *Paragonimus westermani*; m = male and female *Schistosoma*.

Acute pancreatitis

Rare in most tropical countries. Progression to haemorrhagic, necrotizing disease may be rapid with high mortality.

Causes

Gallstones (50%), alcohol abuse (20–25%), other causes of duct obstruction (e.g. *Ascaris*, tumour, hydatid cysts in common bile duct), drugs (e.g. stavudine, sodium stibogluconate and meglumine antimoniate, thiazides, steroids, tetracycline), viruses (mumps, coxsackie, EBV, HAV, HBV), hypercalcaemia, hyperlipidaemia, trauma, scorpion venom, autoimmune diseases, hypothermia.

Clinical features

Abdominal pain and vomiting (90% cases) plus ↑ amylase/lipase are typical. Peritonism may develop, but as the pancreas is retroperitoneal, abdominal signs are often mild. Jaundice may occur due to oedema around the common bile duct. Severe disease may → periumbilical (Cullen's sign) or flank (Grey Turner's sign) discoloration.

Investigations

Serum amylase/lipase (levels peak early and ↓ over 3–4d), U&Es, Ca2+, glucose, fasting lipids, ABG. Exclude other causes of acute abdomen (➲ Acute abdomen, p. 231). USS for gallstones. If patient deteriorating with severe pancreatitis, CT may show pancreatic necrosis requiring surgery.

Treatment

- Resuscitate as for acute abdomen (➲ Acute abdomen, p. 231).
- *Severe pain*: strong analgesia (e.g. morphine 5–10mg 4–6hrly plus prochlorperazine 12.5mg tds IM).
- Broad-spectrum antibiotics.
- Consider surgery (necrosectomy) in very severe cases.
- Following recovery, consider cholecystectomy if gallstones.

Complications

- *Early*: organ failure with AKI, ARDS, DIC, hypocalcaemia (may require albumin replacement or 10mL of 10% calcium gluconate IV slowly). Transient hyperglycaemia.
- *Late (>1wk)*: pancreatic pseudocyst (may resolve spontaneously or require surgical drainage; if it becomes infected, it requires drainage). A few patients develop persisting diabetes mellitus (DM).

Chronic pancreatitis

Destruction of pancreas with atrophy → some permanent loss of exocrine and endocrine function → pain, DM, and malabsorption (steatorrhoea). Chronic alcohol use accounts for many cases.

Chronic calcific pancreatitis

A syndrome of pancreatic calcification associated with both exocrine and endocrine impairment, commonly encountered in the tropics, especially equatorial Africa, southern India, and Indonesia. Aetiology unknown, but genes that ↓ activity of protease inhibitors in pancreas are risk factors.

Clinical features Chronic malabsorption with weight loss, often with DM (10% of diabetes in East and West Africa) and pain, sometimes severe. Association with pancreatic malignancy.

Management Diabetic control, low-fat diet, and enzyme supplementation (e.g. pancreatin; dose tailored to individual patient).

Biliary disease

Gallstones

Problems arise when gallstones impact. In tropical regions, pigmented gallstones may be more common than in non-tropical regions, due to ↑ haemolysis (e.g. from malaria).

Biliary colic

- *Clinical*: severe, constant pain lasting up to several hours, radiating to the interscapular region, often accompanied by nausea and vomiting. Complications include acute cholecystitis and ascending cholangitis.
- *Management*: strong analgesia and antispasmodics (e.g. hyoscine butylbromide 20mg IV/IM, repeated after 30mins if necessary).

Acute cholecystitis

Acute inflammation of the gallbladder (90% caused by gallstones but also consider biliary parasites).

- *Clinical*: fever and local peritonism, tender, palpable gallbladder especially on inspiration (+ve Murphy's sign), and/or jaundice.
- *Management*: treat with broad-spectrum antibiotics (e.g. ceftriaxone + metronidazole) as inflammation may be associated with infection; usually followed by cholecystectomy when the patient's condition allows.

Ascending cholangitis

Bacterial infection of the biliary tract, usually a result of bile stasis due to chronic obstruction from gallstones or biliary parasites.

- *Clinical*: right upper quadrant (RUQ) pain, fever, and jaundice (Charcot's triad).
- *Management*: broad-spectrum antibiotics as for acute cholecystitis. Biliary drainage may be needed. Consider cholecystectomy when well.

Biliary parasites

Biliary parasites are an important concern in tropical regions (Fig. 6.17). They comprise ascariasis (➲ Ascariasis, p. 269), and liver flukes: fascioliasis (➲ Fascioliasis, p. 285), opisthorchiasis, and clonorchiasis (➲ Opisthorchiasis and clonorchiasis, p. 284).

AIDS cholangiopathy

Biliary obstruction resulting from infection-related strictures of the biliary tract, usually seen with low CD4 count. RUQ pain and cholestasis +/− low-grade fever. May present with asymptomatic cholestatic jaundice. Cryptosporidiosis, CMV, and microsporidiosis are common causes, but often no organism is identified. ART improves prognosis.

Cholangiocarcinoma

Bile duct cancer. Liver flukes are endemic in the Far East and can cause chronic irritation resulting in ↑↑ risk of cholangiocarcinoma in endemic regions (➲ Liver flukes, p. 284).

- *Clinical*: become symptomatic when biliary drainage obstructed, → painless jaundice. May also see ↓ weight & abdominal pain.
- *Management*: staging, surgery. Prognosis is generally poor.

Liver flukes

Opisthorchiasis and clonorchiasis

Millions of people are infected by the closely related human liver flukes *Clonorchis sinensis* (eastern Asia; 35 million infected), *Opisthorchis viverrini* (lower Mekong basin in Thailand, Laos, Cambodia; 10 million infected), *O. felineus* (Europe and northern Asia (esp. Siberia); 1.2 million infected), and *O. guayaquilensis* (Ecuador) (Fig. 6.19). In Northeast Thailand, where the prevalence of *O. viverrini* infection reaches up to 25%, it contributes to the high incidence of cholangiocarcinoma.

Life cycle and transmission

See Fig 6.18. Infection follows ingestion of raw or undercooked fresh water fish containing metacercariae. Adult flukes can live in the biliary tree for years. Ova are shed into the bowel and reach faecally contaminated fresh water, where the miracidia hatch and develop in intermediate snail hosts. Subsequently the metacercariae attach to scales of fresh water fish.

Clinical features

Pathology results from bile duct inflammation caused by large numbers of adult flukes. Infected may present with RUQ pain, anorexia, dyspepsia, diarrhoea, and bloating. Fever, eosinophilia, obstructive jaundice, ↓ weight, ascites, and oedema occur in more severe cases. Some patients have a sensation of something moving within the liver. Asymptomatic hepatomegaly is common. USS may reveal gallbladder enlargement with sludge and gallstones.

Complications

Gallstones and intrahepatic stones are common complications. Risk of cholangiocarcinoma due to *O. viverrini* infection is related to worm burden (5-fold ↑ risk for mild infection, 15-fold for heavy infection). Acute opisthorchiasis (*O. felineus*) causes fever, tender hepatomegaly, splenomegaly, and eosinophilia soon after exposure to a large dose of metacercariae.

Diagnosis

Usually by detection of eggs in stool (may not be present if complete biliary obstruction or low worm burden). See colour plate 8. Adult worms may be identified by ERCP or during surgery. Serology (+/– stool antigen detection assays) available in some endemic areas.

Management

Praziquantel 25mg/kg tds for 2d.

Prevention

- Improved sanitation and prohibition of the use of sewage ('night soil') in fishponds.
- Cook freshwater fish thoroughly; avoid consumption of raw fish.
- Saturated salt solution recommended for fish storage (unproven).
- In non-endemic areas, suspect import of dried or pickled fish.
- Molluscicidal control of snail vectors not currently feasible.

Fascioliasis

Primarily an infection of animals, with humans an 'accidental' host. Nevertheless, >2 million people worldwide are infected with *Fasciola hepatica* or *F. gigantica*. Outbreaks of fascioliasis have involved individuals who chew the stimulant leaves of khat (*Catha edulis*), which is grown under irrigation in Yemen and elsewhere.

Life cycle and transmission

See Figs 6.20 and 6.21. Adult flukes live in the biliary tree of the 1° hosts (usually sheep for *F. hepatica* and cattle for *F. gigantica*), passing eggs that are excreted in faeces; see Colour Plate 8a. In water, ciliated miracidia hatch and infect an intermediate snail host. Free-living cercariae leave the snails, attaching to plants such as watercress where they become metacercaria. Following ingestion, the metacercariae excyst in the duodenum and migrate through the small intestinal wall into peritoneum. Reaching the liver, larvae penetrate the liver and migrate to the common and hepatic ducts, maturing into adult flukes.

Clinical features

Although many infections are asymptomatic, the pre-patent larval stage lasting 3–4mths may be accompanied by abdominal pain, weight loss, fever,

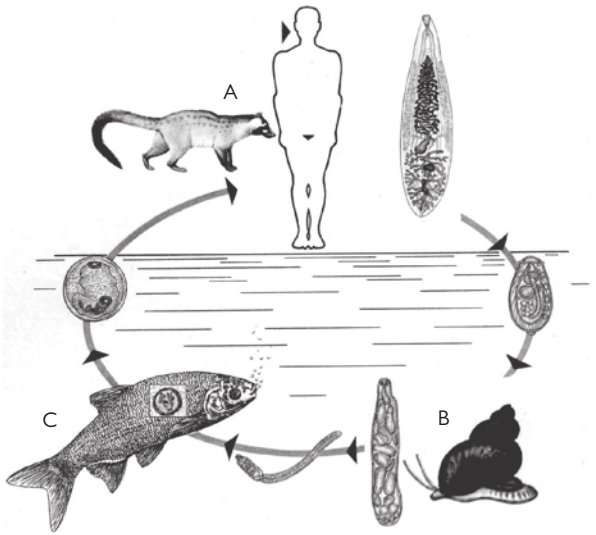


Fig. 6.18 Life cycle of *Opisthorchis* or *Clonorchis*: (A) adult flukes living in biliary tree of carnivorous host (e.g. man or palm civet) shed ova into bowel. Sewage contaminates fish ponds where freshwater snails (B) live. In snails, the parasites develop into miracidia, redia, then cercariae, infecting freshwater fish (C). Carnivore completes cycle, ingesting metacercariae in the flesh of uncooked fish. Adapted from Piekarski, G, *Medical Parasitology in Plates*, 1962, with kind permission of Bayer Pharmaceuticals.

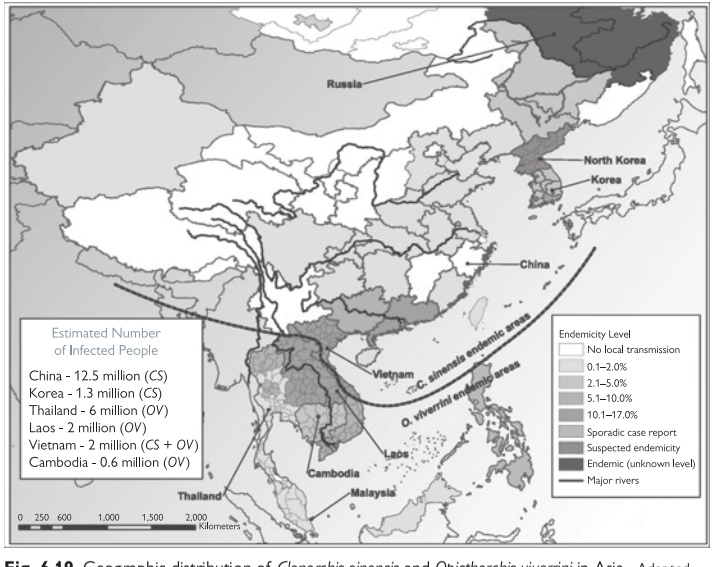


Fig. 6.19 Geographic distribution of *Clonorchis sinensis* and *Opisthorchis viverrini* in Asia. Adapted from International Agency for Research on Cancer (IARC), (2012); reproduced from WHO Press, International Agency for Research on Cancer, with permission

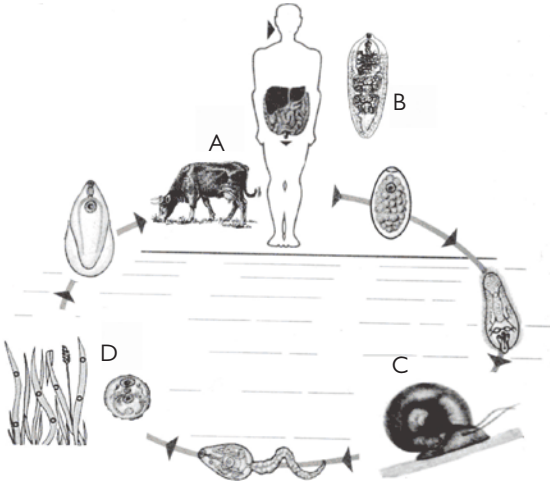


Fig. 6.20 Life cycle of *Fasciola hepatica*. Mammalian hosts (A), usually cattle, sheep, or man, become infected when ingesting aquatic plants (e.g. watercress) or grasses at edges of freshwater. The ingested metacercariae excyst to form young flukes, which migrate through the wall of the intestine and through capsule of liver and liver parenchyma until they reach a large bile duct. There adult fluke (B), 2–4cm long, lives for many years, passing its large (140μm) operculated eggs via the bile duct into the faeces. The eggs hatch in freshwater and undergo development in pond snails (C) into cercariae. These attach themselves to aquatic plants (D), which are ingested to complete the life cycle. Adapted from Piekarski, G, *Medical Parasitology in Plates*, 1962, with kind permission of Bayer Pharmaceuticals.

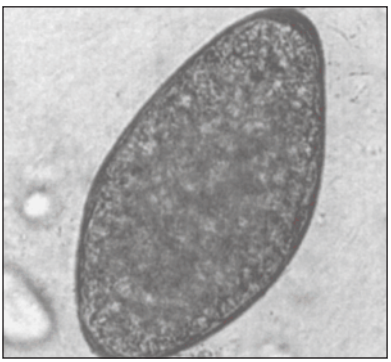


Fig. 6.21 *F. hepatica* egg in a faecal smear (7140 × 50μm).

and eosinophilia. During chronic or biliary stage fascioliasis, a small number of the adult flukes live in the bile ducts and shed eggs into the faeces. Patients are frequently asymptomatic, but may have symptoms and signs of biliary pain or obstruction.

Diagnosis

Eggs can usually be seen in the faeces but first appear 2–4mths after infection—see colour plate 8. Serology is useful for diagnosis. There may be eosinophilia, and USS +/– CT may be suggestive. As juvenile flukes migrate across liver to bile ducts, heterogeneous hypodensities are seen on USS, which migrate with time. Similar anomalies are seen on CT. USS may show fluke within bile ducts. Dietary history is important, particularly in outbreaks and in returning travellers.

Management

Single-dose triclabendazole 10–20mg/kg oral is the treatment of choice. Consider hyoscine to reduce GI spasm. The second-line drug is bithionol, which requires 10–15d of treatment and causes side effects in up to 50%. Praziquantel is *not* active against *F. hepatica*.

Prevention

- Avoid eating raw watercress, khat, and other aquatic plants, especially from grazing areas.
- Exclude animals from commercial watercress/khat plantations.
- Avoid the use of livestock faeces to fertilize water plants.
- If practicable, treat livestock.
- Consider molluscicides to eliminate molluscs (not considered feasible in most settings).

Liver disease

Jaundice

Jaundice (icterus) is visible if plasma bilirubin >35μmol/L. Sclerae and skin appear yellow. Do not confuse normal pale brown sclerae in dark-skinned people with jaundice. Carotenaemia (due to eating excess mangoes, tomatoes, or carrots) also → yellow skin, esp. palms and soles, but the sclerae are white.

Classified according to the site of the problem (Box 6.13; for neonatal causes of jaundice, see ➔ p. 290).

- *Pre-hepatic jaundice*: high circulating *unconjugated* bilirubin usually due to haemolysis. Unconjugated hyperbilirubinaemia may also result from impaired hepatic conjugation (Gilbert's and Crigler–Najjar syndromes) or uptake (rifampicin, right heart failure). Unconjugated bilirubin does not enter urine (acholuric).
- *Hepatocellular jaundice*: hepatocyte damage +/– cholestasis.
- *Obstructive (cholestatic) jaundice:* ↓ bile excretion due to intra- or extrahepatic biliary obstruction → ↑ *conjugated* bilirubin. ↑ urinary excretion of water-soluble conjugated bilirubin → dark urine; stools pale as less bilirubin excreted in faeces. Steatorrhoea (fatty, pale, offensive stools that often float) may occur, and malabsorption of fat-soluble vitamins (A, D, E, K) may → osteomalacia and coagulopathy. Pruritus common (look for excoriations).

Assessment

- Ask about alcohol use, blood transfusions, sexual activity, tattoos, body piercing, jaundiced contacts, family history, and drugs, including herbal medicines.
- Examine for hepatomegaly, signs of chronic liver disease (CLD), encephalopathy.
- Investigations depend on clinical features, but include urine dipstick for bilirubin; FBC, clotting, blood film, Coombs test, U&Es, LFTs, hepatitis viral serology. Liver USS may show dilatated bile ducts (obstructive jaundice), gallstones, hepatic metastases, or pancreatic mass.

Hepatomegaly

Hepatomegaly is common in the tropics. Look for jaundice and signs of CLD. Palpate liver, noting texture, and percuss to define size (normal liver is <12cm in mid-clavicular line). Auscultate for hepatic bruit (typically in hepatocellular carcinoma (HCC), alcoholic hepatitis) or peritoneal rub over liver (may be present in metastases, liver abscesses). Feel carefully for an enlarged spleen which may accompany hepatomegaly in many situations.

Causes

Consider all the causes listed for hepatocellular jaundice (Box 6.13), CLD/cirrhosis (Box 6.13), and treatable causes of hepatomegaly without jaundice (Box 6.14). Also consider infiltrative conditions (amyloid, sarcoid), Budd–Chiari syndrome, and congestive cardiac failure.

Box 6.13 Important 'tropical' causes of jaundice beyond the neonatal period

Pre-hepatic

- Malaria—not always pre-hepatic, complicated malaria would be hepatocellular too.
- G6PD deficiency.
- Sickle cell disease.
- Gilbert's syndrome.

Hepatocellular

- Viruses, e.g. hepatitis A–E, EBV, CMV, herpes simplex, yellow fever, Lassa fever.
- Other infections, e.g. typhoid, *Leptospira*, *Bartonella*, syphilis.
- Alcoholic hepatitis.
- Chronic liver disease/cirrhosis (➲ Box 6.16, p. 301).
- Drug induced.
- Malignancy: hepatic metastases or HCC.
- Liver abscess.
- Malaria.
- Trypanosomiasis (East African).

Post-hepatic (obstructive)

- Gallstones.
- Pancreatic cancer.
- Porta hepatis lymph nodes.
- Cholangiocarcinoma.
- Primary biliary cirrhosis.
- Sclerosing cholangitis.
- Viral hepatitis (cholestatic phase).
- AIDS cholangiopathy.
- Ascariasis.
- Liver flukes.
- Choledochal cyst or biliary atresia (if missed in infancy).

Box 6.14 Treatable causes of hepatomegaly without jaundice

Infections

- Amoebic liver abscess.
- Schistosomiasis*.
- Miliary TB*.
- Malaria*.
- Visceral leishmaniasis*.
- Plague (*Yersinia pestis*).
- Trypanosomiasis*—typically jaundiced if East African trypanosomiasis.
- Liver flukes.
- Toxocariasis.
- Hydatid disease.
- Bartonellosis.

Cardiac and nutritional

- Beriberi.
- Chagas' disease.
- Kwashiorkor.

* = splenomegaly characteristically present.

Viral hepatitis

Hepatitis A virus (HAV)

Non-enveloped RNA picornavirus. Transmission is by faeco-oral ingestion via contaminated food or water. It is the commonest viral hepatitis worldwide, with childhood infection very common in areas of poor sanitation. In hyperendemic areas most adults have immunity (e.g. India 99%), thus HAV is an uncommon cause of acute hepatitis in adults in these settings. Frequently affects non-immunized travellers; 2° cases or outbreaks in affluent countries may follow importation.

Clinical features

- HAV severity is proportional to age: asymptomatic infection is common in children, fulminant hepatitis can occur in adults (<1%).
- Presents after a 2–6wk incubation period with fever, malaise, anorexia, nausea, abdominal discomfort, myalgia, headache, arthralgia.
- Symptoms improve as jaundice appears. Jaundice may be cholestatic and may persist for several weeks, esp. in adults.
- Hepatosplenomegaly may occur, and occasionally lymphadenopathy or a rash.
- Virus is excreted in the faeces 1–2wks before onset of jaundice and for 1–2wks after; some children may excrete virus for 1–2mths.
- Persistent infection and chronic liver disease do not occur.

Diagnosis

HAV IgM is detectable at symptom onset; HAV IgG rises 1–2wks later and remains detectable for life (= lifelong immunity). ALT/AST rise at the onset and typically settle in 2–6wks.

Treatment

Supportive—most infections are self-limiting. Avoid alcohol until LFTs return to normal.

Prevention

Improved sanitation ↓ transmission. Vaccination strategies vary from routine provision to targeted at people with ↑ risk of infection, most notably travellers to endemic areas.

Hepatitis E virus (HEV)

Non-enveloped, RNA herpesvirus, which is endemic at a low level in many parts the world. Transmission and clinical features resemble HAV. Unlike HAV, most adults are non-immune: thus, isolated cases or outbreaks affecting adults occur. In India, HEV accounts for >50% sporadic hepatitis in adults. Like HAV, most infections are self-limiting. Women in the 3rd trimester of pregnancy may have fulminant liver failure and death (>20%) for reasons that are poorly understood. Diagnosis is via HEV IgM, and treatment is supportive. A subunit vaccine is available but to date (2018) is only registered in China.

Hepatitis B virus (HBV)

HBV, a double-stranded DNA hepadnavirus, is an important cause of acute and chronic hepatitis and HCC. Worldwide, 2 billion people show serological evidence of exposure and >250 million have active infection. Highest

prevalence areas for chronic HBV infection are sub-Saharan Africa, China, and SE Asia.

Transmission

HBV is in blood and (to a lesser extent) in semen, vaginal secretions, and saliva of actively infected individuals. Main modes of transmission are (1) vertical (mother-to-child) transmission perinatally; (2) via infected blood products, unsterilized needles etc.; and (3) sexually. Horizontal transmission in the family via close contact including child-to-child is also important. High-risk groups include health workers, haemophiliacs, IV drug users, haemodialysis patients, those in institutions, and MSM.

Natural history of HBV infection

- Most infections are asymptomatic, esp. in infants and young children.
- Symptoms occur after an incubation period of 1–4mths.
- Acute HBV is indistinguishable from other acute viral hepatitides. Fulminant hepatitis occurs in <1%, and when occurs may require liver transplantation. Glomerulonephritis is a rare complication.
- Following acute HBV infection, there is either complete recovery (with long-term immunity) or persistent infection. The latter occurs in <5% infected as adults, 30% infected as children, and 90% infants infected at birth; it is more common in the immunocompromised.

Serological markers of infection

Following infection, there is marked viraemia. HBsAg becomes detectable after 4–10wks, followed by IgM anti-HBc. As the host immune response targets infected hepatocytes, ALT ↑, and HBeAg (which is a marker of active viral replication) becomes detectable. Recovery with viral clearance is accompanied by disappearance of HBsAg and appearance of anti-HBs and anti-HBe antibodies. During the 'window' period between disappearance of HBsAg and appearance of anti-HBs, acute infection can be confirmed by presence of anti-HBc (Fig. 6.22).

Persistent infection See Fig. 6.23. Defined as presence of circulating HBsAg >6mths post infection. Manifests as either:

- *Asymptomatic chronic HBV carriage* (persistent viraemia but normal ALT and normal/near-normal liver histology), *or*
- *Chronic hepatitis B* (liver function and histology abnormal). Symptoms are usually non-specific and do not correlate with disease severity. 20% of patients eventually develop cirrhosis, and there is a 100-fold ↑ risk of HCC.

HBV DNA quantification is the most direct and sensitive marker of ongoing viral replication; persistent HBeAg also indicates higher levels of replication. Clearance of HBeAg may occur with development of anti-HBe, may be accompanied by a transient ↑ ALT and clinical hepatitis (due to immune-mediated destruction of infected hepatocytes) and brief viraemia. ~1% of patients with chronic infection per year will clear the virus permanently and remain immune thereafter.

Management of acute HBV infection

Supportive; avoid alcohol.

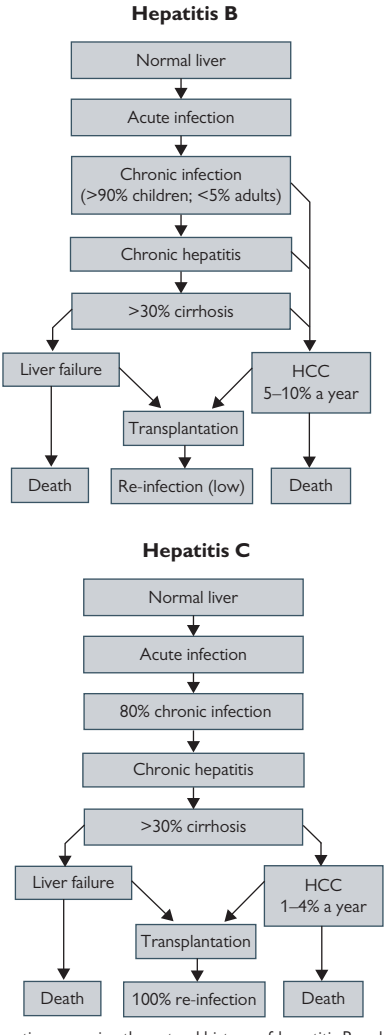


Fig. 6.22 Schematic comparing the natural history of hepatitis B and C infection. Reprinted with permission from *The Lancet*, 384 (9959), Christian Trépo, Henry L Y Chan, and Anna Lok, Hepatitis B virus infection, pp. 2053–2063, https://doi.org/10.1016/S0140-6736(14)60220-8 © 2014 Elsevier Ltd. All rights reserved.

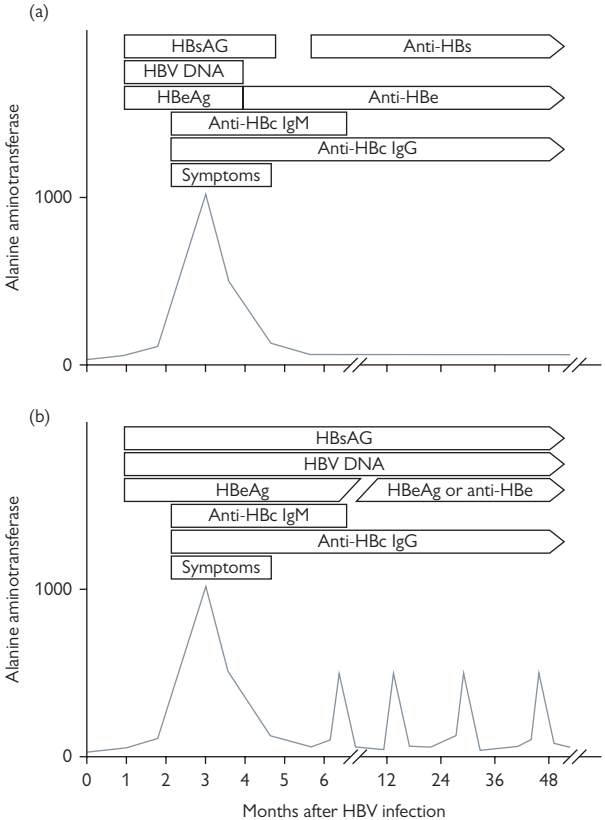


Fig. 6.23 Serological changes in chronic HBV infection. (A) HBV asymptomatic chronic carriage. (B) Chronic hepatitis B. HBsAg (HBV surface antigen); anti-HBs (specific IgG against HBV surface antigen); HBeAg (HBV e antigen); anti-HBsAg (specific IgG HBsAg); anti- HBc IgM/IgG (specific IgM/G to HBV core antigen). Reprinted with permission from *The Lancet*, 2006, 368: 896–7, with permission of Elsevier.

Management of chronic HBV infection

- WHO advocates anti-HBV treatment for all individuals with evidence of cirrhosis (e.g. APRI >2.0 in adults (Box 6.15), and for non-cirrhotic adults with (1) age >30yrs, (2) persistently ↑ ALT, and (3) high-level HBV replication (e.g. HBV DNA >20,000 IU/mL).
- Test for HIV and consider ART in all HIV/HBV co-infected individuals with severe chronic liver disease regardless of CD4 count.
- First-line treatment options for adults and those aged >12yrs are tenofovir and entecavir (nucleoside analogues with a higher barrier to resistance than, e.g. lamivudine). Entecavir is recommended in children

Box 6.15 Estimating degree of hepatic fibrosis

Where access to treatment is limited, non-invasive tests for hepatic fibrosis may guide resource allocation. Aminotransferase/platelet ratio index (APRI) >1.5 has 92% specificity for significant fibrosis with 39% sensitivity. These patients should be prioritized for treatment. Patients with an APRI score <0.5 may have treatment deferred as they have a low risk of cirrhosis (18%). FIB-4 is a similar scoring system—calculators are available online. Other non-invasive measures of fibrosis include US elastography (e.g. FibroScan®). APRI is also used in decision-making regarding HBV treatment, where a more stringent cut-off of 2.0 is used, indicating high risk of cirrhosis.

$$\text{APRI} = \frac{\text{AST (IU/L) / AST ULN (IU/L)}}{\text{Platelets } (10^9/\text{L})} \times 100$$

IU/L, international units/Litre; ULN, upper limit of normal.

2–11yrs. In the context of HIV coinfection, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is preferred option to initiate ART (in patients >3yrs).

- Treatment is generally lifelong; relapses frequently occur with treatment interruptions. Discontinuation may be possible in exceptional circumstances in individuals without cirrhosis, who have evidence of viral clearance, and who can be closely monitored.
- Monitor regularly for HCC (every 6mths if cirrhotic), disease progression, and drug toxicity (annually if stable).
- Assess alcohol intake and try to ↓ moderate/high intake. Promote healthy lifestyle (nutrition, exercise etc.). Avoid drugs that may ↑ viral replication or have hepatic toxicity (e.g. steroids, NSAIDs).

Prevention of HBV

- Immunization with hepatitis B vaccine is recommended by WHO for all infants. Immunization has → ↓↓ prevalence of infection in young children from 4.7% in the pre-immunization era to 1.3% in 2015.
- The first dose should be given as soon as possible after birth, preferably within 24h, followed by two or three further doses to complete the primary series (if complete, booster vaccine is not required).
- Immunization is also recommended for high-risk groups incl. healthcare workers, travellers to endemic areas, and those with specific exposure risks.
- PEP should be given to babies born to mothers who are HBV carriers and to non-immune individuals exposed to HBV (e.g. needlestick injury). PEP involves active immunization *and* passive immunization with hyperimmune hepatitis B immunoglobulin within 12h of birth or as soon as possible after exposure (dose: adults 500IU, children 5–9yrs 300IU, children <5yrs, infants 200IU).

Hepatitis D virus ('delta agent')

Single-stranded RNA virus that can only replicate in the presence of HBV, and is transmitted by similar routes. 5% of chronic HBV carriers are

HDV co-infected, especially in the Mediterranean region, parts of eastern Europe, Africa, the Middle East, and South America. Co-infection → more severe acute HBV hepatitis or, in chronic HBV infection, accelerated hepatic failure and cirrhosis. Treatment and prevention are as for HBV (HBV vaccination prevents HDV co-infection).

Hepatitis C virus (HCV)

Enveloped, single-stranded RNA flavivirus with six major genotypes and >50 subtypes. Transmission is mainly blood-borne via injecting drug use, reuse or inadequate sterilization of medical equipment, and transfusion of infected blood products. Iatrogenic infection is common: in Egypt, regional HCV prevalence rates >15% are attributed to previous mass parenteral anti-schistosomal treatment programmes. Less commonly, sexual and vertical transmission may occur. Risk of infection following needlestick injury from an HCV +ve donor is 2%.

The development of multiple highly effective direct-acting antiviral treatments capable of achieving cure rates >95% have revolutionized HCV care. WHO has set ambitious targets to diagnose 90% of infected individuals and provide treatment to 80% of those eligible by 2030 (2015 baseline, 20% and 7%, respectively). ↑ access to diagnostic services and treatment in high-burden areas over the coming years will make reference to local protocols, and utilization of local expertise, essential.

Natural history

1° HCV infection usually gives no or mild, flu-like symptoms, and 15–20% of patients will clear the virus without treatment. >80% develop chronic HCV infection, which → non-specific symptoms, e.g. malaise, nausea, and abdominal pain, but is associated with chronic hepatitis → cirrhosis, which occurs in 7–18% after 20yrs. Progression is faster with alcohol abuse, obesity, in males, those infected at an older age, with HIV co-infection (especially if immunosuppressed) and/or HBV co-infection, and those with HCV genotype 1. Once cirrhosis present, the risk of HCC is 3–7%/yr. Extrahepatic manifestations, which are uncommon, include glomerulonephritis, cryoglobulinaemia with vasculitis, and lichen planus.

Diagnosis

- HCV IgG becomes detectable 6–8wks after infection.
- HCV RNA PCR is used to confirm chronic infection (i.e. exclude spontaneous clearance).
- Viral genotyping helps guide the choice of antiviral regimen, though this may be less important in the future with the advent of direct-acting antiviral regimens effective against all genotypes.

Management

- Assess alcohol intake and support alcohol reduction for individuals with moderate/high intake.
- Address other high-risk behaviours (e.g. IV drug use) if present.
- Screen for HIV and treat if appropriate.
- Vaccinate for HBV and HAV.
- Assess the degree of fibrosis. All individuals chronically infected with HCV should be considered for treatment, but where access to treatment is limited, those with significant fibrosis and/or cirrhosis

should be prioritized. If liver biopsy is not possible, consider using non-invasive APRI or FIB-4 indices (Box 6.15).

- Direct-acting antiviral-based treatment regimens are superior to interferon/ribavirin (which remains an alternative in some cases). Choice of regimen depends on availability, viral genotype, presence of specific contraindications for the various agents, and required monitoring schedule. This is a rapidly changing area. Although full discussion is beyond the scope of this text, WHO guidance (2016) on preferred regimen choice is provided for reference (Table 6.2).
- In advanced disease, consider screening for varices and HCC.

Table 6.2 WHO preferred regimens for HCV treatment

Genotype	Cirrhosis	Preferred regimen(s)
1	No	Daclatasvir[a]/sofosbuvir[b] *Or* ledipasvir[b]/sofosbuvir[b]
1	Yes	Daclatasvir[a]/sofosbuvir[b] +/− ribavirin[c] *Or* ledipasvir[b]/sofosbuvir[b] +/− ribavirin[c]
2	Yes/no	Sofosbuvir[b]/ribavirin[c]
3	No	Daclatasvir[a]/sofosbuvir[b] *Or* sofosbuvir[b]/ribavirin[c]
3	Yes	Daclatasvir[a]/sofosbuvir[b]/ribavirin[c]
4	No	Daclatasvir[a]/sofosbuvir[b] *Or* ledipasvir[b]/sofosbuvir[b]
4	Yes	Daclatasvir[a]/sofosbuvir[b] +/− ribavirin[c] *Or* ledipasvir[b]/sofosbuvir[b] +/− ribavirin[c]
5/6	Yes/no	Ledipasvir[b]/sofosbuvir[b]

[a] Contraindicated with concurrent use of drugs influencing CYP3A.

[b] Contraindicated in renal failure, amiodarone co-administration, and p-glycoprotein (gp) inducers.

[c] Contraindicated in pregnancy, breastfeeding, females not on contraception, and in the context of a multitude of other severe medical problems.

Alcohol and drug-induced hepatitis

Alcoholic hepatitis

Clinical features

Jaundice, nausea/vomiting tender hepatomegaly, hepatic bruit may be present. The systemic inflammatory response to liver damage causes fever, malaise, anorexia, and ↑ WBC. Signs of CLD/cirrhosis may also be present.

Investigations

↑ liver enzymes (AST >ALT), ↑ bilirubin, ↑ ALP, ↑ WBC. Alcohol excess per se may →↑ GGT and MCV, and ↓ platelets. ↓ hepatic synthetic function in cirrhosis → ↓ albumin, ↑ PT.

Management

- Abstinence from alcohol is key.
- Manage alcohol withdrawal with reducing course of benzodiazepine (e.g. chlordiazepoxide).
- Optimize nutrition (aim at 1.5g protein/kg and 30–40kcal/kg body weight) and give high-dose B vitamins (Pabrinex®) IV.
- Look carefully for infection: culture blood, urine, and ascitic fluid if present, consider *Clostridium difficile* colitis.
- Objective severity scoring e.g. using MELD and MDF scores (calculators available online, e.g. http://www.alchepscores.com) give prognostic information.
- If severe alcoholic hepatitis and no evidence of sepsis, consider prednisolone (40mg od for 28d). This is controversial, recent studies failed to demonstrate any long-term benefits, and weigh up potential benefit against side effects of steroids (esp. serious infections) in resource-limited settings. Biochemical scoring at 7d can help to determine those who will not respond and for whom treatment should be stopped (Lille model). Contraindications to steroids incl. active infections (e.g. sepsis, TB, HBV), GI bleeding, renal failure, pancreatitis.

Prognosis

Approx. 20% mortality at 28d, 40% by 6mths. Abstinence from alcohol and good nutrition improve survival.

Drug-induced hepatitis

Important cause of liver disease because may be severe, even fatal, but often reversible with cessation of the offending agent (Table 6.3). Clinical and biochemical features may mimic almost any other form of liver disease. May occur as a predictable consequence of a drug with known hepatotoxic effects (e.g. paracetamol overdose), or as an idiosyncratic reaction, which occur infrequently, at therapeutic doses, and with variable latency period albeit with a pattern of injury that is (generally) characteristic for each drug).

Clinical assessment

Careful drug history including traditional and herbal medicines or over-the-counter drugs, noting the timing of symptoms in relation to start of drug. Antimicrobials, especially anti-TB, anti-HIV, and antiparasitic medications, are common causes of drug-induced liver injury. The presence of jaundice in drug-induced liver injury carries serious significance.

Table 6.3 Drugs causing liver injury

Type of liver injury	Candidate drugs
Acute necrosis	Paracetamol, aspirin, cocaine, niacin
Acute hepatitis	Isoniazid, pyrazinamide
Cholestatic hepatitis	Rifampicin, penicillins, co-amoxiclav, cephalosporins, sulfonylureas
Mixed hepatitis	Antiepileptics, NSAIDs
Enzyme elevations without jaundice	Isoniazid, antiretroviral agents, methotrexate, aspirin, paracetamol
Acute fatty liver with lactic acidosis	IV tetracycline, aspirin, linezolid, antiretrovirals (nucleoside analogues)
Non-alcoholic fatty liver	Corticosteroids, antidepressants, antipsychotics
Chronic hepatitis	Isoniazid, propylthiouracil, nitrofurantoin, minocycline, fibrates, statins, hydralazine, methyldopa

Suggested key/exemplar agents from Livertox (http://livertox.nih.gov) have been adapted to focus on agents relevant to resource-limited settings and do not represent a comprehensive list.

Rule out other common causes, e.g. viral or alcoholic hepatitis. *Livertox* is an online resource with comprehensive information on reported liver toxicities of drugs (including some herbal supplements etc.): see http://livertox.nih.gov/.

Management

The drug should preferably be withdrawn altogether; often a fatal outcome can be traced back to the patient being given further doses of medication (e.g. TB drugs) after the onset of liver injury. If drugs cannot be withheld, the patient requires very closely clinical and biochemical monitoring for signs of progressive liver damage with a full consideration of the risk/benefit of continued treatment (e.g. nevirapine hepatotoxicity on starting ART). A decision to re-challenge will depend on severity of the liver reaction, availability of alternative drugs, and on the indication for drug's use. For example, when deciding whether to re-challenge with antituberculous drugs, one should take into account confidence of initial TB diagnosis, clinical severity of TB, and duration of TB therapy already received.

Chronic liver disease and cirrhosis

CLD common in the tropics due to alcohol consumption, HBV and HCV, and parasites, e.g. schistosomiasis, bacteria, and toxins. Persistent liver injury → cirrhosis: irreversible destruction of liver cellular architecture by fibrosis, with nodular regeneration of hepatocytes. Causes are shown in Box 6.16.

Clinical features

Variable, according to degree of liver damage and compensation. Symptoms include malaise, pruritus, bleeding, abdominal swelling, and drowsiness (if encephalopathic). May have hepatomegaly in early cirrhosis, although liver typically shrinks as fibrosis progresses. Examine for jaundice, and extrahepatic signs of CLD including portal hypertension (PHT) and hepatic encephalopathy:

- *CNS*: encephalopathy (drowsiness, flapping tremor, constructional apraxia = cannot copy a five-pointed star).
- *Face and skin*: jaundice, hepatic fetor, excoriations.
- *Hands*: leuconychia, clubbing, palmar erythema, bruising, Dupuytren's contracture.
- *Chest:* gynaecomastia, loss of body hair, spider naevi, bruising.
- *Abdomen*: splenomegaly, ascites, testicular atrophy.
- *Legs*: oedema (due to hypoalbuminaemia), muscle wasting.

Hyponatraemia occurs due to 2° hyperaldosteronism, and osteomalacia may occur due to ↓ 25(OH) vitamin D.

Diagnosis

↑ ALT/AST/ALP indicates hepatocellular damage (pattern often dependent on aetiology); ↓ albumin and ↑ PT indicate ↓ liver synthetic function. USS often shows characteristic cirrhotic liver architecture. Liver biopsy (check PT, platelet count, and Hb before biopsy) confirms diagnosis and may give clues to cause.

Management and prognosis

Depends on severity and underlying cause. Cirrhosis is irreversible; aim is to limit further damage, treat complications, and support patient.

- Avoid alcohol and hepatotoxic drugs (e.g. paracetamol). Avoid NSAIDs, sedatives, and opiates.
- Treat dehydration and intercurrent infections.

Box 6.16 Causes of chronic liver disease/cirrhosis

- Chronic alcohol abuse.
- Chronic HBV or HCV infection.
- Genetic disorders (haemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease).
- Non-alcoholic steatohepatitis.
- Autoimmune: autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), PBC.
- Hepatic vein events (e.g. Budd-Chiari syndrome).
- Drug induced.
- Haemosiderosis.

- Ensure adequate nutrition.
- Treat ascites.
- Screening, management, and prevention of PHT (➲ Portal hypertension, p. 304) and variceal bleeds (➲ Oesophageal varices, p. 229).
- Colestyramine 4–8g od oral if severe pruritus.
- If possible, treat underlying cause, e.g. periportal fibrosis in hepatic schistosomiasis is partially reversible with praziquantel treatment.

Hereditary haemochromatosis

Inherited disorder of iron metabolism →↑ intestinal iron absorption → iron deposition in multiple organs incl. liver, heart, pancreas, pituitary, adrenals, skin, and joints. Inheritance is usually autosomal recessive. Most common genetic mutation occurs in Northern Europeans.

Clinical features

Classic triad of hyperpigmentation, hepatomegaly, and diabetes (30–50%). Fatigue and arthralgia are early symptoms. Presentation is usually in the 4th–6th decade, due to slow accumulation of body iron. Patients have ↑ susceptibility to infections and may present with sepsis. Men are more frequently and severely affected, probably due to female menstrual iron loss.

Diagnosis

Consider in case of elevated ferritin with ↑ transferrin saturation >80%, ↑ serum iron, ↓ TIBC. Check LFTs, blood glucose, ECG +/– echo. Joint X-rays may show chondrocalcinosis. Liver biopsy can assess severity of liver disease. Differential diagnosis includes haemosiderosis (below) and other causes of 2° iron overload (e.g. thalassaemia and sideroblastic anaemia); other causes of CLD (see earlier in section); and porphyria cutanea tarda.

Management

Venesection ↓ morbidity/mortality of haemochromatosis. Remove 1 unit blood (500mL, 250g iron) weekly initially, until mildly iron deficient; then maintenance venesection of 1 unit every 2–3mths. Maintain serum ferritin <50ng/mL and transferrin saturation <50%.

Haemosiderosis

Haemosiderosis (a focal or general ↑ in tissue iron stores) occurs in southern Africa (and to a lesser extent in other areas) and is caused by chronic ingestion of traditional beer brewed in iron containers. Formerly called 'Bantu siderosis', condition is becoming less common as commercial products replace traditionally brewed beer. Co-factors for CLD commonly coexist, e.g. high alcohol intake and HBV infection.

Clinical features

Incl. hyperpigmentation, hepatomegaly (portal fibrosis/cirrhosis), and cardiac failure. Vitamin C deficiency is often present. Associated osteoporosis may → vertebral collapse.

Manage as for hereditary haemochromatosis, with regular venesection. Plastic containers for brewing and storage of beer ↓ disease progression/occurrence.

Primary biliary cirrhosis (PBC)

Chronic granulomatous cholangiohepatitis → destruction of interlobular bile ducts. Aetiology is autoimmune. 90% of PBC patients are female. Associated with thyroid and pancreatic disease, Sjögren's syndrome, and scleroderma.

Clinical features

Fatigue, hepatosplenomegaly, clubbing, xanthomata, xanthelasma, arthralgia, and features of cholestasis, cirrhosis, and PHT.

Diagnosis

Often diagnosed following incidental discovery of abnormal LFTs. ↑ ALP, ↑ GGT, slightly ↑ AST/ALT; ↑ bilirubin in late disease. Perform liver USS to exclude extrahepatic biliary obstruction. Antimitochondrial antibodies are highly specific. Liver biopsy and/or ERCP confirm diagnosis.

Management

Symptomatic: colestyramine for pruritus, low-fat diet, and vitamin supplementation. Monitor for signs of portal hypertension. Death commonly occurs within 5yrs in severe disease.

Wilson's disease

Rare, autosomal recessive disorder of copper excretion → toxic accumulation of copper in liver and brain.

Clinical features

Tremor, dysarthria, dyskinesias, parkinsonism, and eventually dementia; Kayser–Fleischer rings (greenish-brown pigment at corneoscleral junction) are pathognomonic, but may only be seen with a slit lamp and are often absent in young children.

Diagnosis

↓ serum caeruloplasmin levels, ↑ 24h urinary copper excretion. Liver biopsy shows ↑ copper (but also ↑ in chronic cholestasis). MRI may show typical changes in basal ganglia.

Management

Lifelong penicillamine chelation. Screen first-degree relatives.

Indian childhood cirrhosis

Affects children aged 1–3yrs in Indian subcontinent. It may follow a subacute, acute, or fulminant course, ranging from a viral type acute hepatitis to cirrhosis. Mortality is high, though progression to HCC is rare. Cause is unknown, although high copper intake (e.g. from milk stored in copper vessels), +/– an inherited defect of copper absorption/metabolism has been implicated. No specific treatment.

Portal hypertension

PHT may be a sequel to any chronic liver disease, although cirrhosis and schistosomiasis are common causes in the tropics. Categorize causes according to the level of obstruction (Box 6.17).

Clinical features of PHT

Signs of CLD should be present. ↑ portal pressure → splenomegaly and ascites; development of portosystemic venous collaterals → oesophageal/gastric varices (most serious complication), caput medusae (distended collateral veins radiating from the umbilicus), and haemorrhoids.

Management of PHT

- Treat underlying cause where possible.
- Manage and prevent oesophageal variceal bleeds (➲ Oesophageal varices, p. 220).
- Prompt treatment of SBP (Spontaneous bacterial peritonitis) and hepatorenal syndrome (➲ Liver failure, p. 306).
- Transjugular intrahepatic portosystemic shunting (TIPS) is an option where available, but expensive and shunt stenosis is common.

Ascites

Ascites occurs in PHT due to a combination of sodium and water retention (splanchnic arterial vasodilation and ↓ splanchnic arterial pressure, ↑ release of vasoconstrictors and antinatriuretic factors), ↑ portal hydrostatic pressure, and ↓ plasma oncotic pressure (↓ albumin) (Box 6.18).

Management

Improve cirrhosis and PHT, give specific treatment to ↓ ascites:

- *Moderate ascites*: give low-dose diuretics (spironolactone 50–200mg od or amiloride 5–10mg od); if response poor or peripheral oedema present, add furosemide 20–40mg od for the first few days. Aim for 300–500g weight loss/day (800–1000g if peripheral oedema).
- *Massive ascites (rapid accumulation with abdominal discomfort)*: drain ascites with plasma expander cover (e.g. 20% albumin 100mL IV per litre drained); remove drain within 24h to minimize infection risk. High-dose diuretics are a less effective alternative (spironolactone 400mg od plus furosemide 160mg od oral). Irrespective of which method used, diuretics should be used to prevent re-accumulation.
- *Refractory ascites*: repeated ascitic drainage 2–4wkly; consider TIPS.

Spontaneous bacterial peritonitis

Spontaneous infection of ascitic fluid, usually with intestinal pathogens (e.g. *E. coli*) occurs in 10–30% of patients with ascites. There may be abdominal tenderness or signs of sepsis, but often asymptomatic/non-specific presentation: consider in any patient with ascites who deteriorates. HRS complicates in up to 30% of episodes.

Diagnosis

Microscopy and culture of ascitic fluid: SBP defined as >250 polymorphonuclear cells/mm^3.

Box 6.17 Causes of portal hypertension

Pre-hepatic

- Hyper-reactive malarial splenomegaly (↑ portal blood flow).
- Portal vein occlusion (e.g. lymphoma, pancreatic cancer).
- Portal vein thrombosis (e.g. severe dehydration).
- Splenic vein occlusion (following neonatal umbilical sepsis).

Hepatic (sinusoidal)

- Cirrhosis.
- Schistosomiasis (*S. mansoni* or *S. japonicum*).
- HCC.
- Veno-occlusive disease.
- Congenital hepatic fibrosis.
- Drugs (e.g. dapsone).

Post-hepatic

- Congestive cardiac failure (e.g. rheumatic fever, TB pericarditis).
- Endomyocardial fibrosis.
- Inferior vena cava obstruction.
- Hepatic vein thrombosis (Budd–Chiari syndrome).

Box 6.18 Common causes of ascites

- Portal hypertension (see Box 6.17 for causes).
- Abdomino-peritoneal TB.
- Hypoproteinaemia (e.g. nephrotic syndrome).
- Right heart failure.
- Constrictive pericarditis.
- Chylous ascites.
- Malignancy (e.g. ovarian cancer).

Treatment

Broad-spectrum antibiotics (e.g. ceftriaxone) pending culture results. Consider 2° prophylaxis (e.g. ciprofloxacin 500mg od oral) as recurrent episodes common (70% at 1yr). Albumin (1.5g/kg initially and 1g/kg at 48h) ↓ the incidence of HRS.

Veno-occlusive disease

Thrombosis of smaller hepatic veins due to toxins in certain herbal teas (e.g. *Heliotropium*, *Crotalaria*, and *Senecio*). It is an important cause of PHT in Jamaica, South Africa, Central Asia, and Southwest USA.

Liver failure

In the tropics, liver failure usually results from viral hepatitis or alcohol. Less common causes include drug-induced hepatitis (TB treatment, paracetamol overdose), other infections (e.g. yellow fever, leptospirosis), acute fatty liver of pregnancy, and toxins (e.g. from mushrooms). Onset may be acute with no preceding illness or jaundice (fulminant hepatic necrosis). However, liver failure occurs more commonly in patients with pre-existing cirrhosis. Patients undergo chronic deterioration with infection, lethargy, GI bleeds, ↑ diuretic usage, and/or electrolyte disturbances.

Clinical features

Include jaundice, fetor hepaticus (breath smells like ammonia or musty), hypoglycaemia, sepsis (which may be overwhelming), ascites +/− SBP, coagulopathy, hepatic encephalopathy, and HRS.

Hepatic encephalopathy

Liver failure → ↑ ammonia, which enters the brain where astrocytes clear it, producing glutamine in the process. ↑ osmotic pressure due to excess glutamine causes fluid to enter cells ↑ cerebral oedema and hepatic encephalopathy. Early signs incl. lethargy, asterixis (liver flap), constructional apraxia (e.g. inability to copy a five-pointed star), and reversed sleep pattern with diurnal somnolence, which may → confusion, drowsiness, incontinence, ataxia, +/− ophthalmoplegia, extrapyramidal signs, and eventually coma.

Hepatorenal syndrome

HRS occurs in >10% of patients with advanced cirrhosis and ascites, and is thought to be due to severe intravascular hypovolaemia causing renal vasoconstriction. Two types are recognized:

- *Type 1*: characterized by progressive oliguria and rapidly ↑ creatinine, often precipitated by SBP.
- *Type 2*: common in patients with refractory ascites, with gradually ↑ creatinine.

Prognosis is poor. Median survival without treatment <1mth for type 1. Where available, vasopressin analogues (e.g. terlipressin 0.5–2mg bd IV) plus albumin may be effective in patients with type 1 HRS.

Management

- Ideally requires intensive care.
- Monitor vital signs, neurological observations, blood glucose, urine output, weight (if possible).
- Treat hypothermia and hypoglycaemia.
- Monitor FBC, U&Es, LFTs, and clotting.
- Give 10% glucose 1L every 12h to avoid hypoglycaemia if practicable (ensure careful control of fluid balance).
- Insert NGT (unless oesophageal varices) and consider NG feeding.
- Avoid sedatives, hepatotoxic drugs, drugs metabolized by the liver, and NSAIDs (risk of GI bleed).
- Give lactulose (and/or neomycin) to ↓ ammonia absorption from gut.

- Control active bleeding with FFP/platelets; give vitamin K 10mg od IV for 3d to correct PT (less effective in established cirrhosis).
- Manage coma in hepatic encephalopathy (➔ Box 9.1, p. 385) and monitor for signs of ↑ ICP (consider mannitol).
- Investigate and treat suspected infection promptly (e.g. SBP).
- Liver transplant, where available.

Amoebic liver abscess

Amoebic liver abscess (ALA) is the most common form of extraintestinal amoebiasis. Only 10% of ALA patients have diarrhoea at presentation, 70% have no history of dysentery (➲ Acute diarrhoea with blood, p. 105). ALA may present months–years after exposure.

Liquefication of liver and surrounding tissue can → cyst rupture into surrounding anatomical spaces.

- Peritoneal amoebiasis: occurs with abscess rupture into the peritoneum. Occurs in 2–7% of those with a liver abscess.
- Pleuro-pulmonary amoebiasis: occurs with rupture into the pleural space. Resembles bacterial pneumonia with empyema. Hepato-bronchial fistulae may develop with extensive expectoration of liver abscess material.
- Pericardial amoebiasis: occurs with rupture into the pericardium, esp. if the ALA was in the left lobe of the liver. Often → cardiac tamponade and death; adequate pericardial drainage usually requires thoracotomy.
- Brain abscesses and other distal lesions have been reported.

Clinical presentation

- Usually presents acutely with fever, rigors, and RUQ +/− right shoulder tip pain, +/− vomiting. Left lobe abscesses often → LUQ pain.
- May also present subacutely with dull RUQ ache, weight loss, fatigue, low-grade pyrexia, and anaemia. Subacute presentation seems to be common in patients who have taken empiric antimalarials or antimicrobials with some anti-amoebic activity.
- Use of empiric antimalarials may make onset less acute.
- Clinical signs include hepatomegaly (often tender); 'punch tenderness' may be elicited if abscess concealed beneath the ribs.
- Extreme tenderness or oedema of the abdominal wall or intercostal space suggests imminent rupture.
- Right-sided pleural effusion/empyema/lung collapse may occur due to rupture into the pleura.
- Rupture of a left lobe abscess into pericardium usually rapidly fatal.

Diagnosis

- Neutrophilia, ↑ ESR, +/− ↑ ALT/ALP.
- CXR may show raised hemi-diaphragm +/− pleural reaction and/or basal atelectasis.
- USS: large (usually unilocular) necrotic lesion with some internal debris. During the early 'amoebic hepatitis' stage of the disease, USS may miss the lesion: repeat USS after 24–48h may be required.
- *Entamoeba histolytica* serology is +ve in >95% of patients after the first week. See Colour Plate 6b.
- Stool microscopy is +ve for amoebic cysts in 50%.
- Abscess fluid (if aspiration indicated, see 'Management' subsection) is odourless and reddish-brown (resembles 'anchovy sauce') vs yellow pus, often foul-smelling, of bacterial abscesses. Microscopy shows debris (vs pus cells in bacterial liver abscess) and Gram stain does not show organisms; only rarely may *E. histolytica* trophozoites be seen.
- Beware misdiagnosing acute ALA as cholecystitis or appendicitis.

Management

- Historically, drug therapy was found to → healing without scarring in most ALA cases. There is no drug resistance and regimens remain metronidazole 800mg tds (or tinidazole 2g od) oral 5d, followed by diloxanide furoate 500mg tds (or paromomycin 500mg tds) oral 10d for intraluminal *E. histolytic*a cyst eradication.
- When USS is available, diagnosis and treatment of ALA is often enhanced, and made safer, by USS-guided aspiration or percutaneous drainage. Indications for percutaneous drainage are:
  - To avoid rupture in large abscesses which are close to surface of the liver clinically or on USS.
  - Left lobe abscess (risk of rupture into pericardium).
  - Severely ill patients in whom rupture is considered imminent either clinically or on USS.
  - Diagnostic uncertainty (aspirate for Gram stain/culture).
  - Lack of response to drug therapy after 3–4d.
- Remove drain when drainage is minimal (usually after 2–3d).
- Follow up ALA clinically, with rapid resolution of fever and hepatic tenderness being the expected response. WBC, CRP, and ESR can also be used to monitor response. USS often shows very slow (months) resolution of the defect, but this does not indicate treatment failure provided the patient is clinically well.

Liver cancer

Hepatocellular carcinoma

Common, particularly in men aged 20–40yrs, causing ~1 million deaths/yr worldwide. Commonest cancer of men in sub-Saharan Africa, affecting up to 1/1000 men annually in Mozambique. Also common in parts of Asia and the western Pacific.

Aetiology and major risk factors

- Chronic HBV and HCV cause ~80% of HCC.
- Cirrhosis (e.g. 2° to alcohol, although ↑ HCC risk with chronic ingestion of >4.5 units alcohol/day can be independent of cirrhosis).
- Aflatoxin B1 ingestion: toxin produced by the plant mould *Aspergillus flavus*, which grows on groundnuts (peanuts), maize, millet, peas, and sorghum.
- Cigarette smoking.
- Diabetes and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

Clinical features

RUQ pain, weakness, and ↓ weight. Hepatomegaly in 90%, cachexia and ascites in 50%, abdominal venous collaterals in 30%, jaundice in 25%. Hepatic bruit is audible in 50%. Bone metastases may → pathological fractures. There may be evidence of CLD and PHT (e.g. bleeding from oesophageal varices).

Diagnosis CXR may show a raised right hemidiaphragm. ALP and alpha-fetoprotein usually ↑. Other investigations: USS, CT scan, biopsy.

Management

HCC is a rapidly growing tumour. Options include surgical resection for solitary tumour and liver transplantation, but in resource-limited settings, treatment is usually palliative. Presentation may be fulminant, with death occurring within weeks. Relieve pain and ↓ symptoms (e.g. with analgesia, antipruritic agents, drain ascites, transfusions for anaemia).

Prevention

HBV vaccination. ↓ risk factors for HBV/HCV acquisition.

Secondary tumours of liver

Liver metastases signify advanced diseases. Clinical features may relate to the underlying 1° cancer or may be non-specific (e.g. malaise, lethargy, ↓ weight). The liver may have a characteristic knobbly feel on

Box 6.19 Differential diagnosis of the irregular liver

Cystic lesions

- Amoebic or pyogenic abscess: both usually very tender in a febrile, toxic patient.
- Hydatid cysts—usually few symptoms.
- Congenital liver cysts/polycystic liver—usually asymptomatic.
- Polycystic liver—usually asymptomatic.

Solid lesions

- Likely to be malignant.

palpation or a peritoneal rub on auscultation (see box 6.19 for differential diagnosis of irregular liver). Jaundice is relatively uncommon as a presenting feature.

USS and biopsy are the best means of determining the cause of focal liver lesions, and whole-body CT scan may show the 1° tumour, although this is not likely to provide life-extending information except in diagnosing lymphomas.

Common origins of liver metastases incl. stomach, colon, lung, breast, and uterus; more rarely: pancreas, carcinoid, leukaemia, and lymphoma.

Hydatid disease

Echinococcus granulosus is the cause of cystic hydatid disease; much rarer *E. multilocularis* causes alveolar hydatid disease. See Fig. 6.24.

Cystic hydatid disease

E. granulosus is a small (3–6mm) tapeworm, which has only three segments, that lives in the small intestine of dogs, jackals, and foxes. The canine becomes infected by eating the cysts in the liver of a sheep. Eggs passed in canine faeces are infective to humans. Following ingestion, eggs develop into oncospheres which penetrate the intestinal mucosa and pass in the blood or lymphatics to host viscera including the liver (50–70%), lungs (20–30%), other organs, and peritoneal cavity. Oncospheres encyst in host viscera developing into mature larval cysts. These may be multiple and reach massive proportions.

Clinical features

Liver cysts grow ~1cm a year, presenting as masses, rather than acutely. Patients may be asymptomatic or present with symptoms related to expansive growth of cysts, including abdominal pain, hepatomegaly, fever, and jaundice . Hydatid disease may commonly be found incidentally when a patient with cholecystitis or other cause of upper abdominal pain is imaged by USS or CT scan. Lung cysts may present when the cyst contents rupture into an airway and are coughed up.

Complications

Cyst rupture may be accompanied by life-threatening anaphylactic shock; conversely, other cysts collapse or disappear spontaneously. Cholangitis

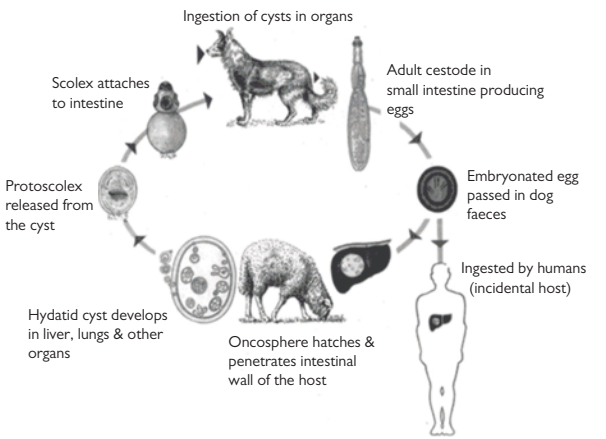


Fig. 6.24 Life cycle of *E. granulosus*. Adapted from Piekarski, G, *Medical Parasitology in Plates*, 1962, with kind permission of Bayer Pharmaceuticals.

may occur due to rupture into the biliary tree. Pyogenic abscesses may form due to bacterial superinfection.

Diagnosis

The characteristic appearance of cysts on imaging (USS, CT, or MRI) is usually sufficient. Serology may aid diagnosis. See Colour Plate 23.

Management

- Some cysts are amenable to percutaneous aspiration–injection–re-aspiration (PAIR) treatment (Box 6.20).
- In addition to PAIR, give albendazole 400mg bd oral for 1–6mths, starting before and continuing after drainage.
- Albendazole treatment alone is not sufficiently reliable, although some individuals with multiple cysts are treated with prolonged courses, sometimes for years, until there is confidence that the cysts are radiologically non-viable. Even after prolonged treatment, cysts may become viable again, and some patients (e.g. with disseminated cysts or bone cysts) may need lifelong follow-up.
- Surgical removal may be necessary for cysts not amenable to PAIR, or which have not responded to PAIR or albendazole therapy, especially if at risk of rupture or exerting pressure effects.

Prevention

- Education and hygiene to avoid exposure to/ingestion of dog faeces.
- In hyperendemic populations, periodic treatment of dogs (including wild and stray dogs) with praziquantel helps to prevent/control human disease.
- Strict control of livestock slaughtering and disposal of organs helps restrict the access of dogs to potentially contaminated viscera.

Alveolar hydatid disease

Occurs mainly in the northern hemisphere. The tapeworm hosts are foxes, and the cysts occur in rodents. *E. multilocularis* → aggressive local tissue invasion by lateral budding of cysts and metastasis to other parts of the body (10% of patients to CNS, lungs, bone, and eyes). Liver complications include cholangitis, Budd–Chiari syndrome, and portal hypertension. Due to the aggressive nature of the lesions, many are misdiagnosed clinically/radiologically as malignancy. Mortality untreated is high (>60% at 10yrs). Operable cases require wide surgical resection. Adjuvant albendazole is of benefit, and in inoperable cases, prolonged albendazole treatment may halt progression of the disease or even cure some patients.

Box 6.20 Percutaneous aspiration–injection–re-aspiration (PAIR)

- Puncture cyst under USS or CT guidance.
- Aspirate >30% of cyst fluid volume.
- Inject* an equal volume of a scolicidal agent, such as hypertonic saline (30% saline = 300g NaCl/L) or 95% ethanol into the cyst.
- Re-aspirate complete cyst contents after 30mins.

** Note*: injection of a scolicidal agent is contraindicated if cyst fluid is bile stained, suggesting communication with the biliary tree.

Chapter 7

Cardiovascular medicine

Ntobeko Ntusi

Bongani Mayosi†

Cardiology in resource-poor countries

Although infectious diseases still dominate clinical medicine in many LMICs, ↑ urbanization, with smoking, hypertension (HT), inactivity, and obesity all → ↑ incidence of diabetes, ischaemic heart disease (IHD), stroke, peripheral vascular disease (PVD), and dementia. HT is likely the single most important cause for cardiovascular disease in LMICs.

'Metabolic syndrome' (➲ Metabolic syndrome, p. 672) refers to a cluster of cardiovascular risk factors including diabetes and ↑ fasting glucose, abdominal obesity, ↑ triglycerides, and ↑ BP. It is associated with physical inactivity, central obesity, insulin resistance, a pro-inflammatory state, and hormonal changes.

IHD is still rare in rural parts of Africa, India, and South America. HT, rheumatic heart disease, TB pericarditis, cardiac infections (e.g. Chagas' disease and HIV), and other cardiomyopathies remain major problems.

Acute rheumatic fever and rheumatic heart disease are common causes of heart failure in children and young adults. HIV co-infection → ↑↑ TB pericarditis, with a mortality of ~40% in HIV+ve patients. Cardiomyopathies are endemic in many LMICs, e.g. peripartum cardiomyopathy and endomyocardial fibrosis.

Chagas' disease is a major cause of 2° disability in young adults in Latin American countries. Congestive cardiac failure (CCF) caused by Chagas' cardiomyopathy is the most frequent and severe clinical manifestation of *Trypanosoma cruzi* infection, and has a worse prognosis than heart failure due to other causes.

Cardiovascular disease in Africa and in many other LMICs has great social and economic relevance owing to its high prevalence, mortality, and impact on young, economically active individuals. There is an urgent need for population-based studies of cardiovascular disease in LMICs and studies of interventions that will ↓ morbidity and mortality from non-ischaemic and ischaemic cardiovascular disease.

Cardiac arrest and advanced life support

Most sudden deaths result from arrhythmias associated with acute myocardial infarction (MI) or chronic IHD. In younger people, myocarditis and cardiomyopathy are important causes of sudden cardiac death. Other causes include hypotension (e.g. blood loss, anaphylaxis, drugs), cardiac tamponade, tension pneumothorax, pulmonary embolus, and respiratory arrest.

Diagnosis of cardiac arrest

Cardiac arrest is confirmed by the lack of a central pulse (carotid or femoral arteries) and absent heart sounds. Agonal breathing may continue for a few minutes, but the arrested patient rapidly becomes cyanotic and loses consciousness. 1° respiratory arrest will quickly be followed by cardiac arrest without urgent respiratory support.

Successful cardiopulmonary resuscitation is most likely if:

- The arrest is witnessed.
- Basic life support (BLS) is started promptly.
- Defibrillation (if appropriate) is carried out as early as possible.

Basic life support

The purpose of BLS is to maintain adequate ventilation and circulation until the underlying cause can be reversed. Ensure it is safe to approach patient, and remember A, B, C—Airway, Breathing, Circulation:

Airway Remove any foreign bodies from the airway (including false teeth); use suction if necessary. Tilt the head back (unless a neck injury is suspected) or do jaw thrust.

Breathing Is the patient breathing? If not, use bag and mask ventilation (with 100% O_2) if available, or mouth-to-mouth resuscitation, until intubation possible. If upper airway obstruction, consider cricothyrotomy. Treat any tension pneumothorax before proceeding further.

Circulation Is there a carotid/femoral pulse? If not, begin chest compressions until defibrillator attached (see following subsection on advanced life support (ALS)).

If alone and the patient is unconscious, assess whether going for help would be of more benefit than attempting resuscitation alone. It is hard to leave an injured/unconscious person, but their only realistic hope of survival may be if you go straight for help.

Advanced life support

ALS is aimed at identifying and treating reversible causes of cardiac arrest, including defibrillation of 'shockable' rhythms (Fig. 7.1)—ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT).

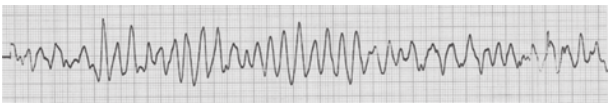
➲ The ALS algorithm is included in the inside rear cover of this handbook for ease of reference in an emergency.

ALS training is essential for those performing ALS, since improper use of defibrillators could result in harm to patient or clinician. It is strongly recommended that medical staff familiarize themselves with the ALS manual (or equivalent) and practise ALS simulations.

Automated external defibrillators automatically assess the cardiac rhythm and give verbal instructions to the resuscitation team so are easier to use. However, training in their use is still required.

Intubation and IV access should take <30s. If difficult, they should be delayed until the next cardiopulmonary resuscitation cycle. If defibrillation remains unsuccessful, consider changing the paddle positions or defibrillator. If a spontaneous pulse is felt at any stage, stop chest compressions (continue ventilation as appropriate), check BP, and do a 12-lead ECG.

(a)



(b)

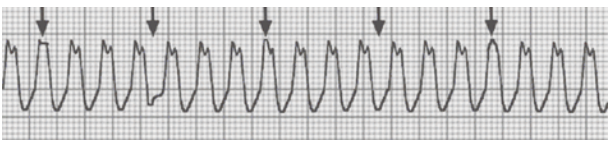


Fig. 7.1 Shockable rhythms: VF and (pulseless) VT. Reproduced with permission from Saul G. Myerson, Robin P. Choudhury, and Andrew R. J. Mitchell (eds), *Emergencies in Cardiology* 2e, 2009, Oxford University Press.

Chest pain

Chest pain is a common presenting complaint with a large number of potential cardiac and non-cardiac causes. The history is key to identifying the likely aetiology.

Central chest pain

Nature of the pain

- A constricting pain suggests angina, oesophagitis, or anxiety.
- A sharp ('pleuritic') pain suggests pleural or pericardial pain. Both may ↑ on deep inspiration, chest movement, or change in positions.
- Prolonged, crushing, ('like an elephant on my chest'), intense pain unrelated to position/breathing suggests MI (may be atypical in women or absent in diabetics or heart transplant recipients).
- Pain radiating to the back may indicate aortic dissection.

Pains that are unlikely to be cardiac in origin:

- Short, sharp, stabbing or pricking pains.
- Pains lasting <30s, however intense.
- Well-localized left submammary pain.
- Pains of continually varying location.
- Pains that are reproduced on chest palpation (suggests musculoskeletal cause).

Ask about

- Radiation to shoulders, neck, jaw, or arms, especially left: suggests lesion of the heart, aorta, or oesophagus.
- Precipitating/exacerbating factors: exercise, emotion, or palpitations suggest ischaemia; food, lying flat, hot drinks, or alcohol suggests oesophagitis.
- Alleviating factors (*note*: glyceryl trinitrate (GTN) relieves both angina and oesophageal pain—action usually more rapid in angina).
- Position: pericardial pain often improves on leaning forward.
- Dyspnoea and/or palpitations, pallor, sweating, feeling of doom, nausea/vomiting: may → MI but can occur with GI pathology.
- Risk factors for IHD (age >55yrs, previous angina/MI, smoking, DM, HT, hyperlipidaemia, and family history).

Other causes of chest pain

Other causes of chest pain are summarized in Box 7.1.

Box 7.1 Causes of chest pain

Cardiovascular	*Pleuro-pericardial*
• Angina. • MI. • Aortic dissection. • Aortic aneurysm. • Large pulmonary embolus. • Tumours (primary).	• Pericarditis. • Pleurisy. • Pneumothorax. • Pneumonia.
Airway	*Chest wall*
• Intubation. • Central bronchial carcinoma. • Inhaled foreign body. • Tracheitis.	• Rib fracture. • Rib tumour. • Muscular strain. • Thoracic nerve compression. • Costochondritis. • Thoracic varicella zoster. • Coxsackie B infection.
Mediastinal	*Other*
• Oesophageal spasm. • Oesophagitis. • Mediastinitis. • Sarcoid or TB lymphadenitis. • Lymphoma.	• Anxiety, hyperventilation. • Panic attacks. • Tabes dorsalis. • Gallbladder disease. • Pancreatic disease.

Shock

Shock is inadequate perfusion of vital organs due to ↓ BP.

Clinical features

Tachycardia (unless on β-blockers), thready pulse, ↓ BP, pallor, faintness, sweating, cool peripheries, prolonged capillary refill time.

In fit adults there may be >10% blood loss before ↓ BP falls. Postural hypotension may be present in the early stages of shock.

Cardiogenic shock

May occur rapidly or after progressive heart failure. Causes include arrhythmias, MI, myocarditis, pericardial tamponade, tension pneumothorax, endocarditis, PE, aortic dissection. Carries high mortality.

Management

Treat underlying cause, if known. Give O_2 by mask. Monitor ECG, urine output, ABGs, U&Es. If resources available consider central venous pressure monitoring and inotropes to keep systolic BP >80mmHg.

Hypovolaemic shock

Due to sudden loss of blood (e.g. trauma, ruptured aneurysm, or ectopic pregnancy) or body fluid (e.g. cholera).

Management

Prevent further blood loss. Aim rapidly to restore circulatory volume. Give whole blood where possible (cross-matched if there is time, otherwise use rhesus –ve blood). While waiting for blood to arrive, give warmed crystalloids (e.g. Hartmann's or normal saline).

For guidance on treatment of shock in children see ➔ Circulation and shock, p. 7 and ➔ Management of shock in children with severe malnutrition, p. 12.

Tips on fluid resuscitation

- Use the largest vein and cannula possible.
- Add pressure to the fluid bag to speed the infusion.
- If difficult IV access prevents rapid fluid resuscitation of a haemodynamically unstable patient, don't waste time—insert intraosseous needle (➔ Intraosseous needle insertion, p. 12).
- If all else fails it may be necessary to cut down to a vein (e.g. 2cm above and anterior to the medial malleolus).
- Give extra fluid if there are fractures: ribs 150mL, tibia 650mL, femur 1500mL, pelvis 2000mL. Double these volumes if there are open fractures.
- Remember to splint fractures and apply traction to ↓ blood loss.

Other causes of shock

Endocrine failure

- Addison's disease (➔ Addison's disease, p. 506).
- Hypothyroidism (➔ Hypothyroidism, p. 496).

Septic shock

See ➔ Sepsis p. 678.

Anaphylactic shock
See Box 7.2

Box 7.2 Anaphylaxis

May be caused by insect venom (bee stings), food (eggs, peanuts), drugs (antibiotics, aspirin especially if given IV, vaccines, antivenom, incompatible blood transfusion). Requires rapid treatment of laryngeal oedema, bronchospasm, and hypotension.

Management

- Stop any drug that has caused the anaphylaxis.
- Secure the airway, give O_2.
- Give *IM adrenaline* 0.5mg (0.5mL of a 1:1000 solution): repeat every 5min until BP and pulse both ↑. (Patients on β-blockers may need salbutamol IV for 48h.)
- Give an *antihistamine* (e.g. chlorphenamine 10–20mg by slow IV injection). Continue this orally for 48h.
- Give *IV hydrocortisone* 100–300mg slowly; may need oral steroids tapered for a few days depending on the antigen.
- If deteriorating → additional IV fluids; consider IV aminophylline or nebulized salbutamol. May need assisted ventilation and emergency tracheostomy for laryngeal oedema.

Anaphylactic reactions require prior exposure and sensitization to an antigen, following which even minute antigen exposure may cause anaphylaxis. Skin prick testing can be used to identify culprit antigens.

Anaphylactoid reactions are clinically similar, but follow exposure to large quantities of allergen (e.g. through IV infusion of horse serum antivenoms). Prior skin testing does not identify a subsequent anaphylactoid reaction since reaction is dependent on quantity of antigen injected. *Always have IM adrenaline already drawn up when injecting antivenoms.*

Hypertension

HT is common in LMICs and a major risk factor for MI, stroke, renal and heart failure, and PVD. Treatment of HT aims to ↓ incidence of complications.

Clinical features

Usually asymptomatic until irreversible damage has occurred. Symptoms that may occur include dizziness, fatigue, headache, palpitations. Accelerated ('malignant') HT may present with acute symptoms—see later in topic.

Clinical signs

↑ BP (BP may be normal if heart failure); end-organ damage (e.g. left ventricular (LV) hypertrophy, heart failure, retinopathy, proteinuria, uraemia). In 2° HT, signs of underlying disease may be present.

NB: ensure BP measured twice with correct sized cuff in the sitting position, after at least 5min and preferably 15min relaxing.

Investigations

Measure BP on at least three occasions. Search for cause, particularly in the young. Depending on resources, do U&E, creatinine, glucose, lipids, urinalysis for protein, renal USS, ECG, CXR, fundoscopy. Consider 24h urinary catecholamines if phaeochromocytoma is suspected.

Who to treat

- Treat if systolic BP >180mmHg or diastolic BP >95mmHg on three occasions over 1–2d. Treat immediately if severe HT or complications, e.g. heart failure (Box 7.3).
- If initial BP consistently >140/90mmHg over several weeks *and* no vascular or end-organ complications *and* not diabetic, try lifestyle modifications and reassess in 3mths. If BP still high, start drug therapy. Start drug therapy if vascular/end-organ complications or diabetes.
- Aim for BP <130/80mmHg in diabetics and patients with vascular disease or CKD.
- Treat isolated systolic HT (systolic BP >160mmHg with diastolic BP <90mmHg) in persons >60yrs if persists over 3mths—preferably with low-dose thiazide diuretic +/− low-dose β-blocker.
- HT during pregnancy can be treated with methyldopa; β-blockers and Ca^{2+} channel blockers can be used during the 3rd trimester.

Specific indications for antihypertensive agents

- Carotid atherosclerosis: Ca^{2+} channel blockers.
- CCF: ACE inhibitor, β-blocker, +/− spironolactone (depending on severity of CCF).
- CKD: ACE inhibitor or angiotensin receptor blocker (ARB).
- Diabetes: ACE inhibitor or ARB.
- ECG LV hypertrophy: ARB or ACE inhibitor.
- IHD: β-blockers, long-acting Ca^{2+} channel blockers.
- Resistant HT: spironolactone.
- 2° prevention of stroke: ACE inhibitor plus diuretic or ARB.
- Reserpine: still used; cheap, effective, keep dose <0.5mg/d.
- PVD: *avoid* β-blockers as these exacerbate PVD.
- Gout: if possible *avoid* diuretics, may exacerbate/trigger gout.

Box 7.3 Management of hypertension

Aim to ↓ incidence of stroke, heart and renal failure, and MI.

- *Lifestyle modifications*:
  - Stop smoking.
  - ↓ Na^+, alcohol intake, ↓ weight if obese.
  - ↑ intake of K^+, fresh vegetables, and fruit.
  - ↑ exercise.
  - ↓ psychosocial stress.
- *Drug therapy*: explain rationale and goals of treatment; may need treatment for life, even though no symptoms; and may even feel worse on treatment. Encourage patient to return if unacceptable side effects and not simply to stop taking treatment.

Suggested approach

- Start with a thiazide diuretic (e.g. bendroflumethiazide 2.5mg od oral) as first-line therapy. Check plasma K^+ 4wks after starting.
- If BP not controlled, start ACE inhibitor—or ARB if intolerant of ACE inhibitor.
- Use long-acting Ca^{2+} channel blocker (e.g. modified-release nifedipine 10–40mg oral bd) as second- or third-line therapy.
- If still uncontrolled, add a β-blocker (e.g. atenolol 25–50mg oral od) as fourth-line treatment.
- If HT is still not controlled (<10%), seek expert help before starting centrally acting antihypertensives (e.g. moxonidine, clonidine) or vasodilators (e.g. hydralazine).
- Always try to stop ineffective drugs.

Management of accelerated hypertension

- Bed rest, IV furosemide 40–80mg, IV GTN infusion 5–10 micrograms/min, nifedipine 5mg.
- Aim to ↓ BP over days/hours, not minutes (↑ risk of stroke).
- *Do not ↓ BP in acute stroke unless >220/120mmHg* as it may worsen cerebral ischaemia. If so, lower slowly by 15–20% every 24h.
- Maintenance therapy is with usual drugs used for HT.
- Patients need close monitoring; may need specialist evaluation.
- Dihydralazine should be used with caution.

Accelerated hypertension

Rapidly ↑ BP with end-organ damage. Heralded by rapid-onset heart failure, renal failure, encephalopathy (convulsions/coma), or diastolic BP >140mmHg. Look for hypertensive retinopathy, proteinuria, AKI. Untreated, mortality is 90%; even treated, it may carry a 5yr mortality up to 40%. See Box 7.3 for management.

Angina

Myocardial ischaemia classically presents as central, tight chest pain that may radiate → jaw, neck, or one or both arms +/− associated dyspnoea, pallor, or faintness. Precipitants include exertion, anxiety, cold or a heavy meal; relieved by rest and nitrates. Usually caused by coronary atherosclerosis, but look for valvular heart disease (aortic stenosis, aortic regurgitation, and mitral stenosis), hypertrophic cardiomyopathy, tachyarrhythmias, arteritis, or anaemia. Angina is graded clinically using the Canadian Cardiovascular Society (CCS) grading system (Box 7.4).

Diagnosis

On the ECG: look for ST depression, flattened (or inverted) T waves, and evidence of old infarcts (Q waves). If available, do an exercise ECG 48h after the angina settles. Take blood for FBC and ESR to exclude non-atheromatous causes (see earlier), and cardiac enzymes to exclude MI.

Management

Modify risk factors

Smoking cessation, healthy diet (↓ lipids and ↑ fruits and vegetables), ↓ weight, ↑ exercise. Look for and treat HT, DM, and hyperlipidaemia. Start aspirin 75–150mg od.

Treat angina episodes

Start with GTN 300–600 micrograms sublingually, or as a spray at 0.4mg per dose prn up to every hour.

Antianginal therapy

Start with β-blocker and/or Ca^{2+} channel antagonist; if angina not controlled, add long-acting nitrate, e.g.:

- *β-blocker*: atenolol 50–100mg oral od (contraindicated in asthma).
- *Slow-release Ca^{2+} channel antagonist*: nifedipine modified release 30–90mg oral od; felodipine 5–10mg/d; diltiazem 60mg oral 2–3× daily, ↑ to max. 360mg daily (contraindicated in fertile women). (Avoid short-acting Ca^{2+} blockers as they ↑ cardiac events.)
- *Long-acting nitrate*: isosorbide mononitrate 10–60mg/d (od or bd); isosorbide dinitrate 10–60mg tds. *Note*: need nitrate-free interval of 7h in every 24h.

When drugs fail to control angina (CCS class II–IV; Box 7.4), consider revascularization either by percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CABG).

Unstable angina

New-onset angina of at least CCS class III severity (Box 7.4), or angina that is rapidly worsening and present on minimal exertion, or at rest, or within 30d of MI.

Management

Aspirin, clopidogrel, β-blocker, heparin, and bed rest. If pain persists or recurs or TIMI risk score ≥5 (Box 7.4), refer for specialist assessment/angiography/revascularization.

Box 7.4 Canadian Cardiovascular Society grading of angina

- *Class I*: occurs only with strenuous, rapid, or prolonged exertion.
- *Class II*: slight limitation of ordinary activity, e.g. occurs on walking or climbing stairs rapidly, walking uphill, etc.
- *Class III*: marked limitation of ordinary physical activity, e.g. occurs on walking 1 or 2 blocks on the level, climbing 1 flight of stairs at a normal pace.
- *Class IV*: inability to carry on any physical activity without discomfort—symptoms may be present at rest.

TIMI risk score for myocardial infarction or death

The TIMI score* may be used to risk stratify patients' risk for MI or death. Risk of MI or death ranges from 5% (score 0 or 1) to 41% (score 6 or 7).

Prognostic variable	Point
>2 angina events within 24h	1
Use of aspirin within 7d	1
Age ≥65yrs	1
>3 coronary risk factors	1
Known coronary obstruction	1
ECG: ST-segment deviation	1
Elevated cardiac enzymes	1
Total	7

* Thrombolysis in Myocardial Infarction (TIMI) IIB trial risk score.

Myocardial infarction

Irreversible necrosis of part of the heart muscle, almost always due to coronary artery atherosclerosis.

Clinical features

Pain is usually more severe and prolonged (>30min) than angina, and often associated with nausea/vomiting, sweating, pallor, and distress. In the elderly and diabetics, small MIs may be painless. There may be tachycardia, tachypnoea, cyanosis, and mild pyrexia (<38°C). BP may be ↑, normal, or ↓. There may be signs of complications (e.g. heart failure, pericardial rub, or pan-systolic murmur of mitral regurgitation (MR) or ventriculoseptal defect (VSD)).

Diagnosis

ECG and cardiac enzymes. Diagnosis is based on (1) history, (2) ECG changes, and (3) cardiac enzymes. Classified by ECG into ST-elevation myocardial infarction (STEMI) or non-ST-elevation MI (NSTEMI). Troponins are the investigations of choice.

Other tests

- CXR—look for features of heart failure, ↑ in cardiac size (ventricular aneurysm), or aortic dissection.
- Measure Hb, WBC, platelets; urea, creatinine, Na^+, K^+, and glucose.

ECG changes in MI

An initially normal ECG → tall T waves and ST elevation. STEMI is defined as >2mm in two adjacent chest leads or >1mm in two adjacent limb leads, or new-onset left bundle branch block. Within 24h, the T waves invert as ST elevation resolves. Pathological Q waves (>1 small square in width and >2mm in length) form within a few days and persist in 90%. T-wave inversion may or may not persist. If ST elevation persists, suspect ventricular aneurysm (Fig. 7.2).

Site of infarct

- *Anterior*: changes occur in V2–5.
- *Septal*: changes in V1–3.
- *Inferior*: changes in II, III, and aVF.
- *Lateral*: changes in I, aVL, and V6.
- *Posterior*: reciprocal changes in V1–3: dominant R wave (= inverted Q wave) and ST depression (= inverted ST elevation). May be associated right ventricular (RV) infarct—V4R ECG lead (lead V4 placed in mirror image position over right chest) will show ST elevation.

Non-Q-wave infarcts: (formerly called 'subendocardial infarcts') do not involve the whole thickness of the myocardium → ST changes without Q waves.

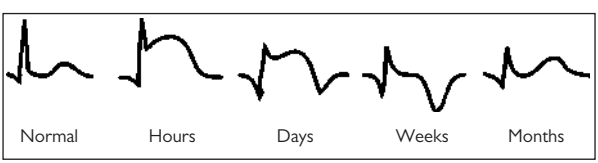


Fig. 7.2 ECG changes following acute ST-elevation MI.

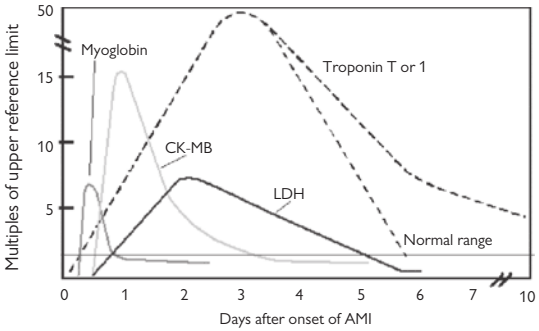


Fig. 7.3. Release patterns of cardiac markers. Wu, A.H., Journal of Clinical Immunoassay 1994; 17: 45–8.

Immediate management of MI

The greatest risk of death is in the 1st hour. Prompt action saves lives.

- Relax and reassure the patient.
- Give O_2 by face mask if hypoxic or left ventricular failure (LVF)/pulmonary oedema suspected.
- Insert IV line; treat pain, e.g. morphine 10mg by slow IV, followed by 5–10mg doses as necessary. Treat nausea with antiemetic.
- Give GTN 0.3–0.6mg sublingual tablet or spray.
- Give aspirin 300mg PO stat, then 75mg od: → 24% ↓ mortality.
- Give clopidogrel 300mg PO stat, then 75mg od (along with aspirin).
- If STEMI, refer for 1° PCI if within 3h of pain onset; or give streptokinase if within 6–12h of pain onset (Box 7.5).
- Give a β-blocker (e.g. atenolol 5mg IV over 5min, 50mg oral 15min later, then 50mg bd) unless the patient has heart failure or asthma. This will ↓ infarct size and risk of arrhythmias and septal rupture.
- Start an oral ACE inhibitor 24h after the MI.
- Start statin in hospital in all patients regardless of cholesterol level.
- Control blood sugar with insulin in peri-MI period (types 1 and 2 DM).
- Prohibit smoking.
- ≥24h bed rest with continuous ECG monitoring and qds vital signs. Examine frequently for complications (➲ Complications of MI, p. 329).
- Daily ECG, cardiac enzymes, U&Es (+ CXR if breathless) for 2–3d.

Post-infarct management

If the post-MI period is uncomplicated, most patients can mobilize by day 2 or 3; be discharged by day 3; and gradually ↑ exercise over 1mth. The patient should not drive during this period. Discourage smoking and give dietary advice.

Prognosis

Depends upon the degree of LV dysfunction +/− pulmonary oedema, presence of significant arrhythmias, heart size on CXR, and presence of post-MI angina. In the UK, mortality rates for the 1st year after discharge are 6–8% with most deaths in the first 3mths.

Box 7.5 Thrombolysis

Streptokinase is the most widely available thrombolytic agent. Give 1.5 million units streptokinase in 100mL 0.9% saline IV over 1h. Carries ~1% stroke risk. Other side effects include hypotension (may respond to slowing or stopping infusion), nausea, vomiting, haemorrhage, anaphylaxis (rare). Tissue plasminogen activator, reteplase, and tenecteplase are more expensive than streptokinase, but slightly more effective and → less hypotension.

Contraindications to thrombolytic therapy

- Stroke or active bleeding (e.g. peptic ulcer) in the last 2mths.
- Systolic BP >200mmHg.
- Surgery or trauma in the past 10d.
- Bleeding disorder or anticoagulation therapy.
- Pregnancy.
- Menstruation.
- Previous streptokinase treatment within the last 1yr.

Long-term treatment

Modify cardiovascular risk factors (see earlier in topic). Indefinite 2° prevention with aspirin, an ACE inhibitor or ARB, and a statin; plus clopidogrel for 9–12mths, and β-blocker for at least 18mths.

Complications of MI

Post-infarct angina (within 30d of MI)

Occurs in up to 30%; associated with ↑ mortality. Manage as outlined previously (➲ Angina, p. 325).

Arrhythmias

See ➲ Cardiac arrhythmias, p. 332.

- *Sinus bradycardia*: may be due to infarct or β-blocker. No action required if haemodynamically stable.
- *Sinus tachycardia*: common after MI.
- *Atrial fibrillation (AF)*: occurs in ~10%. Rate control with β-blocker to avoid VT and infarct extension. Usually transient; if persistent consider conversion to sinus rhythm by DC cardioversion or IV amiodarone (➲ Atrial fibrillation, p. 333).
- *VT*: most common in hours immediately post MI; may be heralded by ventricular premature beats. VT >120bpm may → VF. Treat with IV β-blocker. Correct low serum K^+. Give amiodarone (300mg IV over 20–60min; then 900mg over 24h) if VT persists/recurs.
- *VF*: may occur hours to days post MI. Treatment is DC cardioversion. Often implies poor prognosis.
- *Accelerated idioventricular rhythm*: may occur with reperfusion post thrombolysis; usually benign and does not require specific treatment.
- *Nodal rhythms*: narrow QRS complex with no associated P wave (or P wave after QRS). Usually intermittent and self-limiting. In large MI may ↓ cardiac output and BP. Treat with atropine or temporary pacemaker.
- *Conduction disturbances*: any degree of atrioventricular (AV) block may occur, most commonly in inferior MIs (20%).
  - First-degree block needs no treatment.

- Second-degree block is usually Wenckebach and only requires treatment if there is symptomatic bradycardia.
- Third-degree block often follows second-degree block and is usually temporary. Treat with atropine or isoprenaline if symptomatic.

In extensive anterior MIs, conducting system damage → complete and progressive AV block requiring pacing, possibly permanently. Heart block in inferior MIs is usually temporary, lasting <5d.

Myocardial dysfunction

- *LVF*: see ➲ Left ventricular failure, p. 337.
- *Cardiogenic shock*: severe LVF → hypotension, tachycardia, oliguria, distress, and peripheral shutdown. Causes include acute MR, severe LV dysfunction, cardiac rupture, ventricular septal defect (VSD), arrhythmias, RV infarct. Treat with O_2, IV diuretics (if LVF), fluids (if RV infarct), inotropes.
- *RV infarction*: occurs in a third of inferior infarcts, often not clinically significant. There is ↓ BP and ↑ JVP with clear lung fields on auscultation. Lead V4R (➲ Site of infarct, p. 327) on the ECG may show ST elevation. Treat with IV fluids to ↑ LV filling. Inotropes may be useful.

Mechanical defects

- *Papillary or septal rupture* occurs in <1% of all MIs within a week of anterior or inferior MI. Listen for new murmurs and basal crackles;

Box 7.6 Preventing ischaemic heart disease

Prevention strategies apply to three groups:

- Children and adolescents: lifestyle interventions.
- 1° prevention in adults without overt cardiovascular disease.
- 2° prevention in adults with known IHD, PVD, or stroke.

Lifestyle interventions

- *Diet*: ↑ consumption of fruits, vegetables, whole grains, dairy products, fish, legumes, poultry, and lean meat. Limit salt intake. Fat intake is unrestricted <2yrs. After age 2yrs, limit foods high in saturated fats, cholesterol, and *trans*-fatty acids.
- *Smoking*: avoid starting smoking; complete smoking cessation.
- *Physical activity*: at least 60min/d physical activity; sedentary time must be limited (e.g. limit TV time to <2h/d).
- *Weight*: aim for BMI <25kg/m², and waist circumference <101.6cm in men and <88.9cm in women.

Primary prevention interventions which are cost-effective

- Healthy diet, smoking cessation, physical activity.
- Treatment of HT, DM, and familial hyperlipidaemia.
- Statins in patients with DM and HT with multiple risk factors.

Secondary prevention interventions which are cost-effective

- Healthy diet, smoking cessation, physical activity.
- Statins in patients with IHD, stroke, PVD, and DM.
- ACE inhibitors for patients with MI, PVD, and stroke.
- Cardiac rehabilitation following MI.
- Influenza vaccination.

watch for clinical deterioration. Urgent surgery if papillary muscle rupture with acute MR; early closure of VSD advised.

- *LV aneurysm* occurs in 10–20% of anterior MIs. Apex beat diffuse; there may be atypical/stabbing chest pain, accompanied by ST elevation lasting 4–8wks. Rarely ruptures, but → emboli, arrhythmias, and CCF. Patients may require lifelong anticoagulation. Surgical removal of aneurysm is indicated if intractable heart failure, recurrent VT, and frequent embolism despite anticoagulation.
- *Cardiac rupture* occurs in <1% MIs, usually 2–7d post MI → rapid death. A small or incomplete rupture may be sealed by the pericardium, forming a pseudoaneurysm that needs prompt surgical repair.

Pericarditis

20% of MI patients have a pericardial rub after 24h. Symptoms include chest pain, relieved by sitting up and varying with respiration. Usually self-limiting; single-dose NSAID (e.g. indometacin 100mg pr) may be very effective, avoiding the need for long-term therapy.

Dressler's syndrome An autoimmune pericarditis occurring 1–10wks post MI in 5% of patients. There is fever, ↑ WBC, +/− pericardial or pleural effusion. Treatment is with NSAIDs +/− corticosteroids.

Mural thrombus Common in large MIs and may embolize → stroke or gut/limb/renal infarcts. Diagnosed by echocardiography; needs anticoagulation for 3mths.

Cardiac arrhythmias

Most commonly occur as a complication of acute MI (➲ Complications of MI, p. 329) or chronic ischaemia. Other causes include electrolyte disturbance (K^+, Mg^{2+}, Ca^{2+}), drugs (esp. antiarrhythmics), thyroid disease, myocarditis, and cardiomyopathy.

Clinical features Include palpitations, 'funny turns', pre-syncope, and syncope. Distinguish from epilepsy—a witness may help in this.

Investigations FBC, U&E, Ca^{2+}, glucose, TFTs, CXR, ECG (including ambulatory ECG if available). Echocardiography if suspect cardiomyopathy or valvular heart disease.

Tachyarrhythmias

Broad-complex regular tachycardias are usually due to VT (➲ Complications of MI, p. 329). Narrow-complex tachycardias are commonly due to AF (irregular, no P waves), atrial flutter (regular P waves before each QRS), or AV junctional re-entry tachycardia (regular with no P waves seen or P waves just after QRS; ➲ Nodal rhythms, p. 329).

Management of tachyarrhythmias

- *All haemodynamically unstable tachyarrhythmias*: first-line therapy is DC cardioversion (Box 7.7).
- *VT*: treat with IV β-blocker. Correct low serum K^+. Give amiodarone (300mg IV over 20–60min; then 900mg over 24h) if VT persists/recurs.
- *Paroxysmal re-entry supraventricular tachycardia (SVT)*: If haemodynamically stable, try carotid sinus massage and/or Valsalva manoeuvre. If unsuccessful, give verapamil 5–10mg IV; or adenosine 6mg IV followed by 12mg repeated once if persists. If SVT still persists, use DC cardioversion (Box 7.7).
- *AF*: see following subsection on 'Atrial fibrillation'. If acute onset (<24h) and haemodynamically unstable → DC cardioversion (Box 7.7).
- DC cardioversion may also be used for broad-complex tachycardias and atrial flutter unresponsive to medical therapy (Box 7.7).

Bradycardia

If bradycardia is acute and symptomatic (usually post MI):

- Treat/remove underlying cause (e.g. β-blockers, incl. eye drops).
- Give atropine 0.3–0.6mg slowly IV, repeating to a max. 3mg in 24h.
- Alternatively, try isoprenaline 1–4 micrograms/min IV; ↑ to 8 micrograms/min if required for Stokes–Adams attacks (syncope 2° to arrhythmia).
- Temporary pacing may be needed for unresponsive bradycardia.
- Chronic bradycardia 2° to complete heart block requires permanent pacing.

Box 7.7 Safe DC cardioversion

- Always have full resuscitation equipment at hand.
- Give O_2 via face mask.
- Do 12-lead ECG to check cardioversion is still indicated.
- Sedate patient with IV midazolam boluses until asleep and not responding to name. Have flumazenil ready to reverse sedation.
- *Set defibrillator to synchronized mode* (very important as unsynchronized shocks may → VF in this scenario).
- Apply right paddle under right clavicle adjacent to the sternum, and left paddle against left lateral chest (using electrode jelly as appropriate); apply firm pressure to the pads.
- Set initial energy to 50J.
- Double energy after each unsuccessful shock to max. 360J.
- *Some defibrillators require re-selection of synchronized mode after each shock.*
- Repeat 12-lead ECG post cardioversion.
- Observe patient in high-care area post cardioversion until fully awake and clinically stable.

Box 7.8 CHA_2DS_2-VASc and HAS-BLED scores

CHA_2DS_2-VASc score

- Previous stroke or transient ischaemic attack (TIA).
- Valvular or other structural heart disease.
- Hypertension.
- Diabetes.
- Age >65yrs.
- Left ventricular dysfunction and/or left atrial enlargement on echo.

HAS-BLED score

- **H**ypertension.
- **A**bnormal renal and liver function.
- **S**troke.
- **B**leeding.
- **L**abile INR.
- **E**lderly.
- **D**rugs or alcohol.

Atrial fibrillation

Irregular atrial electrical activity → risk of atrial clot formation (→ stroke) and irregular ventricular contraction → reduced cardiac output. Common causes include IHD, MI, mitral valve disease, HT, hyperthyroidism, excess alcohol; less common causes include other types of cardiomyopathy, pericarditis, sick sinus syndrome, bronchogenic carcinoma, endocarditis, atrial myxoma, and haemochromatosis.

Clinical features An irregularly irregular pulse with a first heart sound of varying intensity and apex rate > radial rate. Patient may be breathless and complain of palpitations. ECG shows a chaotic baseline with no P waves and irregularly irregular QRS complexes.

Therapeutic strategy in AF

- Identify and treat the underlying cause or risk factor for AF.
- Restore and maintain sinus rhythm (rhythm control strategy) or accept arrhythmia and control ventricular rate (rate control strategy).
- Assess thromboembolic risk and anticoagulate patients at ↑ risk.

Rhythm control

DC cardioversion, drugs, ablation, or surgery may be useful in younger patients with structurally normal hearts and paroxysmal AF, or persistent AF of recent onset. Both DC and chemical cardioversion carry risk of embolization of atrial thrombus, so should only be attempted <48h of new AF onset, or once patient adequately anticoagulated for ≥6wks, or precardioversion transoesophageal echocardiogram shows no thrombus.

Rate control

- Appropriate in elderly patients with HT or structural heart disease and persistent AF, esp. if few symptoms.
- Use β-blockers unless contraindicated (e.g. asthma or acute heart failure). Digoxin and Ca^{2+} channel blockers are alternatives.

Anticoagulation

The goal is stroke prevention but this needs to be balanced against the risk of bleeding. Use clinical prognostic scores (e.g. CHA_2DS_2-VASc and HAS-BLED scores; Box 7.8) to estimate an individual's stroke and bleeding risk. Ideally involve patient in decision about anticoagulation.

Syncope

Syncope is transient loss of consciousness (LOC) caused by transient global cerebral hypoperfusion or focal hypoperfusion of the reticular activating system. Cerebral hypoperfusion may be 2° to ↓ cardiac output, ↓ BP, or both. The causes and classification of syncope are summarized in Box 7.9. The differential diagnosis includes trauma, seizures, hypoglycaemia, hypoxia, intoxication, vertebrobasilar TIA, and psychogenic fainting.

Clinical features

Rapid-onset transient LOC lasting seconds to minutes with complete spontaneous recovery. Retrograde amnesia may occur. Syncopal patients may have brief, involuntary clonic movements, but not tongue biting or incontinence.

Clinical assessment

- Identify the cause to evaluate the risk of recurrence or death.
- *Exclude life-threatening causes* including cardiac syncope (arrhythmia or structural), massive haemorrhage, PE, and subarachnoid haemorrhage (suspect if headache precedes syncope).
- *History and examination* (incl. collateral history from witnesses) guides investigations and management:
  - Ask a witness to describe the episode incl. situation, precipitating factors (postural/exertional/situational), prodrome, aftermath.
  - Was there complete LOC?
  - Was the LOC transient, with rapid onset and short duration?
  - Was there spontaneous and complete recovery, without sequelae?
  - Did the patient lose postural tone?
- The answer to all these questions should be 'yes'.
  - Ask about palpitations, other cardiovascular symptoms, previous episodes, medications, and a family history of sudden death.
  - Check vital signs (HR, BP). Examine for pallor, bruits, orthostatic hypotension, arrhythmias, murmurs; muscle weakness; and focal neurology including peripheral neuropathy.
- *Investigations* include:
  - ECG in all patients.
  - Echocardiography to look for LV dysfunction or structural heart disease (e.g. hypertrophic obstructive cardiomyopathy, aortic stenosis).
  - Lying/standing pulse and BP to assess possible reflex syncope or orthostatic hypotension (+/− tilt-table testing).
  - Carotid sinus massage to diagnose carotid sinus hypersensitivity in patients >40yrs of age.
  - ECG monitoring to detect an underlying arrhythmia.

Box 7.9 Classification of syncope

Cardiovascular syncope

Structural

- Cardiac:
  - Valvular heart disease.
  - Acute MI/ischaemia.
  - Hypertrophic cardiomyopathy.
  - Arrhythmogenic cardiomyopathy.
  - Cardiac masses (tumours, myxoma, thrombus).
  - Pericardial disease/tamponade.
  - Congenital anomalies of coronary arteries.
  - Prosthetic valve dysfunction.
- Non-cardiac/vascular:
  - PE.
  - Pulmonary HT.
  - Acute aortic dissection.

Arrhythmic

- Bradycardia:
  - Sinus or AV node disease.
  - Implanted device malfunction.
- Tachycardia:
  - SVT.
  - VT.
  - Implanted device malfunction.
- Drug induced:
  - Bradycardia.
  - Tachycardia.
  - Acute aortic dissection.

Reflex-mediated (neurogenic) syncope

Vasovagal

- Mediated by emotional stress, fear, pain, instrumentation, needle/blood phobia.
- Induced by standing up.

Situational

- Cough, sneeze.
- GI stimulation (swallow, defecation, visceral pain).
- Micturition/postmicturition.
- Post-exercise.
- Postprandial.
- Others (laugh, brass instrument playing, weightlifting).
- Carotid sinus syncope.

Orthostatic syncope

- 1° autonomic failure:
  - Pure autonomic failure.
  - Multisystem atrophy.
  - Parkinson's disease with autonomic failure.
  - Dementia with Lewy bodies.
- 2° autonomic failure:
  - DM.
  - Amyloidosis.
  - Uraemia.
  - Spinal cord injury.
- Drug-induced orthostatic hypotension:
  - Alcohol.
  - Vasodilators.
  - Diuretics.
  - Phenothiazines.
  - Antidepressants.
- Volume depletion:
  - Haemorrhage.
  - Diarrhoea.
  - Vomiting.
  - Dehydration.

Heart failure

A clinical syndrome of effort intolerance, due to a cardiac abnormality, usually with salt and water retention.

Causes

- HT: systemic or pulmonary.
- IHD.
- Heart muscle diseases: cardiomyopathy, myocarditis, infiltration (haemochromatosis, sarcoid, amyloid), Chagas' disease, beriberi.
- Valvular heart disease.
- Pericardial: effusive/effusive-constrictive/constrictive pericarditis.
- Congenital heart disease.
- Other: prolonged tachycardia, thyrotoxicosis, toxins (alcohol, chemotherapy, cocaine), pregnancy, severe anaemia.

Left ventricular failure

LVF → pulmonary oedema → exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, wheeze, cough, fatigue +/− cardiogenic shock.

- *Clinical signs*: ↑ HR, ↑ RR, thready pulse, cold peripheries, ↓ capillary refill, basal lung crackles, third heart sound, pulsus alternans, cardiomegaly, peripheral cyanosis, pleural effusion, wheeze.
- *CXR* signs include cardiomegaly and pulmonary oedema. See Fig. 7.4.
- *ECG* changes will depend on the specific cause.
- *Echocardiography*: myocardial, valvular, and/or pericardial cause.

Right ventricular failure

2° to chronic lung disease ('cor pulmonale') or LVF → peripheral/sacral oedema, abdominal discomfort, nausea, fatigue, and wasting.

- *Clinical signs*: ↑ JVP, hepatomegaly (pulsatile if tricuspid regurgitation), pitting oedema.

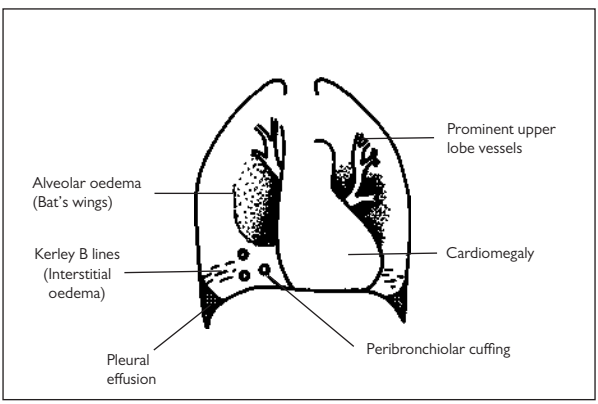


Fig. 7.4 CXR changes in heart failure.

Management

- Treat reversible factors (e.g. anaemia, arrhythmia, electrolyte disturbance, infection, non-adherence to treatment).
- Restrict salt and alcohol intake.
- Avoid NSAIDs (↑ fluid retention; may interact with diuretics and ACE inhibitors and → renal failure).

Drug treatment

- Start diuretic (e.g. furosemide); monitor weight daily and adjust dose to achieve 'dry weight' with ↓ symptoms.
- Once stabilized start ACE inhibitor (Box 7.10), or ARB if ACE not tolerated (angio-oedema, cough).
- Add spironolactone 25–50mg od if available and K^+ not raised.
- Introduce β-blockers cautiously once clinically stable (not in acute severe heart failure), starting at low dose and titrating up dose slowly ('start low, and go slow').
- Consider adding inotrope (e.g. digoxin).
- Isosorbide dinitrate and hydralazine can be effective add-on treatments esp. in African American patients.

Resistant heart failure

Search for other causes; check patient compliance with meds and weighing daily.

Box 7.10 Starting an ACE inhibitor

- Watch for hypotension after the first and second doses.
- If systolic BP <100mmHg, give first doses in hospital if possible.
- Ensure patient not salt or volume depleted (e.g. due to diarrhoea and vomiting).
- Check for aortic stenosis, mitral stenosis, and renal artery stenosis.
- If symptomatic hypotension, give 0.9% sodium chloride infusion (plus atropine if bradycardic).
- *Contraindications*: significant hypotension, angio-oedema, renal artery stenosis, pregnancy, porphyria.

Other precautions

- Check U&Es and creatinine. Urea and Cr will often ↑ when ACE inhibitors or diuretics are first used. Levels will usually plateau and drop later. Monitor closely; stop if Cr/urea ↑ >20% or continue to ↑.
- Weigh regularly to monitor response and train patient to maintain ideal 'dry weight' by adjusting their diuretic dose.
- Beware of drug interactions: Li^+ (levels ↑), digoxin (levels may ↓), NSAIDs (urea and K^+ ↑), anaesthetics (BP ↓).
- Watch for ↓ K^+ derangement from diuretics. Mild hypokalaemia is well tolerated, provided: (1) K^+ >3.5mmol/L, (2) no predisposition to arrhythmias, and (3) no other K^+-losing conditions (e.g. cirrhosis, chronic diarrhoea).

Most patients tolerate ACE inhibitors very well and benefit significantly from them.

Admit to hospital for bed rest, anti-DVT stockings, heparin 5000U SC tds, IV furosemide, and training in use of the weight scale in fluid and symptom management.

- ↑ ACE inhibitor and/or diuretic to max. tolerated dose; consider metolazone where available. Adding a thiazide to a loop diuretic often → synergistic diuresis.
- In extreme circumstances, consider using IV inotropes for a short time (e.g. dobutamine, dopamine).
- Sometimes, a degree of peripheral oedema and exercise limitation must be accepted to avoid unacceptable dehydration.

Rheumatic fever

Rheumatic fever (RF) is an important cause of cardiovascular morbidity and mortality in LMICs. Group A β-haemolytic streptococcal (*Streptococcus pyogenes*) pharyngitis in 3–6% of cases → RF, due to an immune cross-reactivity between the streptococci and connective tissue of heart and synovium (carditis, arthritis), and basal ganglia (chorea).

A disease of the poor, overcrowded, and poorly housed, with children being chiefly affected. Severity in poor countries reflects failure of health services to prevent recurrences of acute RF. If recurrences can be prevented, many patients who have carditis in their first attack will eventually lose their murmurs and have normal or near-normal hearts.

Clinical features

- *Arthritis*: in 80% of RF cases. Typically, an asymmetrical and migratory 'flitting polyarthritis' of large joints; pain is severe while swelling is often modest. Onset is acute and subsides over 1wk; as one joint improves, a second gets worse. This process may continue for 3–6wks. There is a dramatic response to aspirin.
- *Carditis*: in 40–80%. It is the most serious manifestation of acute RF, → death acutely in <1% of cases. It may affect only the endocardium (valvulitis, often MR +/– aortic regurgitation, 'mild carditis'), or the myocardium and pericardium may also be involved ('severe carditis').
- *Chorea*: in 10% after a longer incubation period. Sydenham's chorea is emotional lability and involuntary movements (face, limbs, especially hands). More common in girls; one-third have no cardiac involvement. Seldom affects those with arthritis.
- *Erythema marginatum*: <5% cases.
- *Subcutaneous nodules*: now rare.

Diagnosis

Based upon the revised Jones criteria (Box 7.11) and requires (1) evidence of recent streptococcal infection plus (2) either two major criteria, or one major and two minor criteria.

Management

- Bed rest until child feels better.
- Anti-inflammatory drugs:
  - Aspirin 20–25mg/kg oral qds. Continue for 3–6wks if heart is not involved; 3mths in mild carditis; 4–6mths in severe carditis.
  - Prednisolone 0.5mg/kg qds for 2wks in severe carditis.
- Treat heart failure.
- Treat chorea with sodium valproate 7.5–10mg/kg oral bd for 3mths (alternative: haloperidol 0.05mg/kg od).

Primary prevention of rheumatic fever

Treat suspected streptococcal pharyngitis in children with one dose of IM benzathine benzylpenicillin ↓ by 80% the risk of RF; 60 children need to be treated to prevent one episode of RF.

Box 7.11 Revised Jones criteria

Diagnosis of RF requires:
- Evidence of recent streptococcal infection *plus*
- Either two major criteria, or one major and two minor criteria.

Evidence of recent group A β-haemolytic streptococcal infection
- Positive throat culture or streptococcal antigen test.
- Elevated or rising antistreptolysin O titre.

Major criteria
- Carditis.
- Polyarthritis.
- Chorea.
- Erythema marginatum.
- Subcutaneous nodules.

Minor criteria

Clinical findings
- Arthralgia.
- Fever.

Laboratory findings
- Elevated inflammatory markers (ESR or CRP).
- Prolonged PR interval.

Secondary prophylaxis

Give benzathine benzylpenicillin 1.2 million units (children <30kg, 600,000U) IM every 2–4wks, duration as follows:
- For 5yrs after the last attack of RF, or until age 18yrs, whichever is the longer, for patients without carditis.
- For 10yrs after the last attack of RF or until age 25yrs, whichever is the longer, for patients with mild MR or healed carditis.
- Lifelong prophylaxis is recommended for patients with severe valvular heart disease and after valve surgery.
- Alternative prophylaxis for penicillin-allergic patients: erythromycin 250mg bd PO. Making the IM injection less painful (e.g. use of lidocaine as diluent for penicillin injection), and therefore less frightening for the child, will make 2° prophylaxis more successful.

Infective endocarditis

Fever + regurgitant murmur = infective endocarditis (IE) until proven otherwise. 50% of IE occurs on previously normal valves. When it is caused by highly pathogenic bacteria (e.g. staphylococci, pneumococci, and β-haemolytic streptococci) IE follows an acute course, often with serious emboli, heart failure, and death. The course is more subacute if viridans Streptococci affect valves previously damaged by RF or other causes. IE often occurs on prosthetic valves (2%), in which case the involved valves often need replacing.

Pathogenesis

Any bacteraemia may → colonization of valves. This usually occurs spontaneously, or less often following dental procedures, genitourinary manipulation, or surgery. Gum or tooth infections do not generally → IE, whereas intestinal lesions occasionally do—esp. colon cancer in the case of *Strep. bovis*. Viridans streptococci, *Enterococcus faecalis*, and *Staphylococcus aureus* are common. Rarely fungi, *Coxiella*, or *Chlamydia* spp. infect valves. Gram –ve bacteria (e.g. *Escherichia coli*) almost never cause IE. Rare non-infective causes include SLE and malignancy. Right-sided disease (especially with *Staph. aureus*) is more common in IV drug users and may → pulmonary abscesses.

Clinical features

Evidence of:

- *Infection*: fever, rigors, malaise, night sweats, finger clubbing, splenomegaly, anaemia.
- *Heart murmurs*: esp. regurgitation of aortic or mitral valves; sometimes murmurs change day-to-day—not because the vegetation is changing rapidly, but because fever accentuates the murmur and because valve function may suddenly deteriorate. Usually, murmurs deteriorate until treatment is effective.
- *Embolic events*: vegetations on valves may → emboli, e.g. strokes or acute limb ischaemia. Occasionally, emboli → abscesses or mycotic aneurysms.
- *Vasculitis*: microscopic haematuria, splinter haemorrhages, Osler nodes (painful lesions on finger pulps), Janeway lesions (painful red patches on the palms), Roth spots (on fundoscopy), renal impairment.

Diagnosis

Take three blood cultures at different times. It is not necessary to time cultures with fever spikes, as bacteraemia is relatively constant. Always take blood cultures before starting any antibiotics, delaying antibiotics for a few hours is seldom critical, and a +ve culture will guide therapy. At least one culture will be +ve in 99% of cases. The commonest cause of culture –ve endocarditis is that the patient has received even a single dose of antibiotic prior to taking cultures. Check ESR, FBC, U&E, Cr; echocardiography may show the vegetations on valves; urinalysis for haematuria.

Management

For highly susceptible streptococcal infection (mean inhibitory concentration to penicillin <0.1 micrograms/mL), give benzylpenicillin 1.2g IV every 4h plus synergistic doses of gentamicin 60–80mg IV bd for 2wks. Less sensitive streptococcal isolates require 4–6wks of penicillin plus gentamicin for 2–6wks. For *S. aureus* infections, give flucloxacillin 2g IV every 4–6h and gentamicin as above-mentioned for 2wks, then IV flucloxacillin for a further 2–4wks. Use vancomycin or teicoplanin if methicillin-resistant *Staphylococcus aureus* (MRSA) suspected. For *S. epidermidis* infections (e.g. on prosthetic valve) use vancomycin, gentamicin, and rifampicin for 4wks.

If empiric therapy is required, give benzylpenicillin and gentamicin, and add flucloxacillin if the IE had an acute onset. Change treatment according to blood culture results. This recommendation is based on streptococcal infections being the most common cause of endocarditis. Alter these recommendations according to the local circumstances.

Prognosis

In the UK, 30% mortality from staphylococcal endocarditis, and 6% with sensitive streptococci.

Prevention

The value of antibiotic prophylaxis is uncertain. Traditional guidelines are given in Box 7.12. New guidelines recommend prophylaxis for dental procedures only in patients with underlying cardiac conditions associated with high risk, for procedures involving manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa. Prophylactic antibiotics to prevent IE are not recommended for those undergoing genitourinary or GI procedures (🔗 http://www.ncbi.nlm.nih.gov/pubmed/17446442/).

Antibiotics

- Amoxicillin 3g oral 1h before procedure under local anaesthetic.
- If allergic to penicillin or >1 course of penicillin in last month, give clindamycin 600mg oral 1h before procedure.
- For procedures under general anaesthetic, give amoxicillin 3g oral 4h before procedure and again as soon as possible after procedure.
- For procedures under general anaesthetic in patients at high risk (antibiotics in the previous month, prosthetic valve, or allergic to penicillin), refer all procedures to hospital; use amoxicillin plus gentamicin (or vancomycin in penicillin-allergic patients).

Box 7.12 Traditional guidelines for IE prophylaxis

Traditional guidelines recommended antibiotic prophylaxis for

- Previous history of IE.
- Prosthetic valves.
- Congenital heart disease (except secundum atrial septal defect).
- Valvular heart disease, incl. hypertrophic cardiomyopathy with MR and mitral valve prolapse with regurgitation.
- Surgically corrected shunts/conduits.

Prophylaxis not required for

- Previous CABG.
- Pacemakers/implanted cardiac defibrillators.
- Mitral valve disease without regurgitation.
- Previous RF without valve defects.
- 'Innocent' murmurs.

Procedures requiring prophylaxis

- Dental procedure → bleeding from gum, mucosa, or bone.
- Tonsillectomy.
- Rigid bronchoscopy.
- Incision of abscess.
- Vaginal delivery with chorioamnionitis.
- 'Dirty' surgery/procedure.

Procedures not requiring prophylaxis

- Natural shedding of teeth.
- Caesarean section.
- Vaginal delivery without infection.
- 'Clean' surgical procedures.

Pericardial disease

Pericarditis

In LMICs, this is commonly due to TB or pyogenic infection.

- *TB pericarditis*: common in HIV+ve individuals. Pericardium probably involved from adjacent lymph nodes and pleura. The effusion may be massive in HIV; echocardiogram may show strands of fibrin floating in the effusion.
- *Acute pyogenic pericarditis*: results from bacteraemia from a 1° focus elsewhere (e.g. pyogenic pneumonia).
- *Other causes*: any infection (especially coxsackieviruses), malignancy (e.g. KS in AIDS patients), uraemia, MI, Dressler syndrome, trauma, radiotherapy, connective tissue diseases, and hypothyroidism.

Clinical features

Pericarditis

A sharp, constant sternal pain; may radiate to the left shoulder, down the left arm, or to the abdomen. It is relieved by sitting forward, and worse when lying on the left, coughing, inspiring, or swallowing. Auscultation may reveal a scratchy superficial pericardial rub, loudest at the left sternal edge. In a large effusion, the rub is generally lost, and heart sounds are faint.

Pericardial effusion

If effusion forms quickly, the pericardium cannot stretch → ↑ pressure and compression of the heart → cardiac tamponade. There is ↓ cardiac output (↓ BP), ↑ JVP, Kussmaul sign (JVP ↑ with inspiration), tachycardia, impalpable apex, pulsus paradoxus, peripheral shut down, and quiet heart sounds. In more chronic effusions, signs of heart failure predominate with severe ascites and hepatomegaly. Percussion reveals ↑ cardiac dullness in the retrosternal and right parasternal areas, and the apex beat is impalpable or felt within the area of dullness. Impending tamponade or constriction is first indicated by ↑ JVP; however, JVP may be so high that patient must be examined sitting or standing upright. Patients with pyogenic pericarditis are extremely unwell with signs of severe sepsis.

Diagnosis

ECG in pericarditis classically shows upwardly concave (saddle-shaped) ST segments. In pericardial effusions, CXR shows a large globular heart (+/− pleural effusions). ECG has low voltages and changing QRS complexes (electrical alternans = a changing axis beat-to-beat). See Fig. 7.5. Echocardiography is diagnostic with an echo-free zone showing the heart surrounded by effusion. In exudative effusions, fibrinous strands are clearly seen within the fluid. Differentiate from an MI and PE.

Constrictive pericarditis

Encasement of the heart in a non-expansive pericardium, usually following TB. Features are as for chronic effusion; however, the heart is small on CXR and may show calcification, especially on lateral CXR. Onset is usually insidious, with ascites, oedema, hepatomegaly, and proteinuria being found. The patient may or may not be breathless. Sometimes ↑↑ JVP is missed on routine inspection of the neck.

Management

Pericarditis

- Find and treat cause.
- Give analgesia with NSAIDs if painful.
- For TB pericarditis, commence anti-TB treatment for 6mths and perform HIV test. Adjunctive steroids used to ↓ risk of death or constriction: prednisolone 2mg/kg/d, tapering over 6–8wks.
- *Pericardial effusion*: find and treat cause (e.g. antibiotics for bacterial infections; anti-TB drugs for TB).
- *Tamponade*: requires urgent drainage. Aspirate with a 50mL syringe, fitted with a long needle and two-way tap, inserting upwards and to the left of the xiphisternum. Patient should be propped up 45°. Watch the ECG monitor to know if the myocardium is touched. Steroids are often effective in reducing the reaccumulation of pericardial fluid.
- *Recurrent pericardial effusion*: especially of pyogenic origin, requires surgery draining through a pericardial window or pericardiotomy.
- *Constrictive pericarditis*: requires surgical excision of the pericardium.

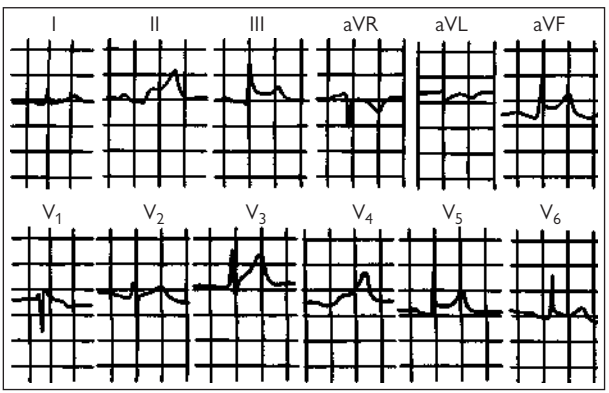


Fig. 7.5 ECG changes in pericarditis.

Myocarditis

Myocarditis is an inflammatory disease of the myocardium, definitively diagnosed on endomyocardial biopsy (EMB). Can be caused by viruses, but rheumatic carditis, Chagas' disease, and advanced HIV are important causes in LMICs (Box 7.13). Few patients undergo EMB, so most are diagnosed by a clinical illness indicating recent-onset inflammatory cardiomyopathy. For management, see Box 7.14.

Clinical features of myocarditis

- Highly variable, from subclinical disease to fatigue, chest pain, heart failure, cardiogenic shock, arrhythmias, and sudden cardiac death. Many likely cases go undetected because they are subclinical or have non-specific signs.
- The variability in clinical presentation reflects the variability in disease severity, aetiology, and disease stage at presentation. Myocardial inflammation may be focal or diffuse, involving any or all cardiac chambers. Severe, diffuse myocarditis can → acute dilated cardiomyopathy.

Box 7.13 Causes of myocarditis

Infectious causes

- Viral (adenovirus, arbovirus, coxsackie B virus, CMV, dengue, echovirus, EBV, hepatitis B and C, herpesvirus, HIV, influenza A and B, mumps, parvovirus, poliomyelitis, rabies, rubella, rubeola, vaccinia, varicella, variola, yellow fever).
- Bacterial (*Bartonella*, brucellosis, *Chlamydia*, cholera, *Clostridia*, diphtheria, gonococcal, *Haemophilus*, *Legionella*, meningococcal, *Mycoplasma*, pneumococcal, psittacosis, *Salmonella*, staphylococcal, streptococcal, tetanus, tuberculosis, tularaemia).
- Spirochaetal (leptospirosis, Lyme disease, relapsing fever, syphilis).
- Fungal (actinomycosis, aspergillosis, blastomycosis, candidiasis, coccidiomycosis, cryptococcosis, histoplasmosis, mucormycosis, nocardia, sporotrichosis).
- Rickettsial (Q fever, Rocky mountain spotted fever, typhus).
- Protozoal (amoebiasis, Chagas' disease, leishmaniasis, malaria, sleeping sickness, toxoplasmosis).
- Helminthic (ascariasis, echinococcosis, filariasis, paragonimiasis, schistosomiasis, strongyloidiasis, trichinosis).

Non-infectious causes

- Cardiotoxins (alcohol, anthracyclines, arsenic, carbon monoxide, catecholamines, cocaine, cyclophosphamide, heavy metals (copper, lead, iron), methysergide).
- Hypersensitivity reactions (antibiotics, clozapine, diuretics, dobutamine, insect bites, lithium, methyldopa, snake bites, tetanus toxoid).
- Systemic disorders (coeliac disease, collagen vascular disorders, granulomatosis with polyangiitis, hypereosinophilia, inflammatory bowel disease, Kawasaki disease, sarcoidosis, thyrotoxicosis).
- Radiation.

Investigations

- Initial testing incl. ECG, cardiac enzymes, and CXR.
- Echocardiogram accurately assesses ventricular function.
- Routine laboratory studies of blood and urine are often normal or non-specific. Measurement of brain natriuretic peptide (BNP) or N-terminal-proBNP is useful if heart failure is suspected.
- Cardiac magnetic resonance imaging has replaced isotope scanning and can reveal features of myocarditis: inflammatory hyperaemia and oedema, necrosis and scars, changes in ventricular size/shape, wall motion abnormalities, and pericardial effusions.
- Coronary angiography in selected patients who may have an acute coronary syndrome.
- EMB is recommended for patients with new-onset heart failure or features of severity.

When to suspect myocarditis?

- Because clinical presentation of myocarditis is highly variable, a high index of suspicion is needed.
- Suspect myocarditis if: (1) onset of otherwise unexplained heart failure, cardiogenic shock, or arrhythmias; (2) age typically 20–50yrs; (3) a history of a viral illness or rash and eosinophilia following a new drug or vaccine; and (4) acute or subacute LV systolic dysfunction without apparent cause.

Differential diagnosis

- IHD, valvular heart disease, other types of cardiomyopathy, congenital heart disease, and pulmonary disease.

Box 7.14 Management of myocarditis

- Treat heart failure and arrhythmias.
- Consider anticoagulation.
- Severe patients with refractory heart failure should be considered for mechanical circulatory support and transplantation.
- Physical activity should be restricted to ↓ the work of the heart.
- Antiviral, immunosuppressive, and IV immunoglobulin therapies should be considered in patients with lymphocytic and giant cell myocarditis.

Cardiomyopathies

Disease of the myocardium → cardiac dysfunction → heart failure, arrhythmia, and sudden death.

Dilated (congestive) cardiomyopathy

Cause may not be identifiable, but includes alcohol, unrecognized HT, pregnancy, HIV, previous myocarditis, or familial/genetic cause.

Clinical features

- Are of heart failure.
- Apex diffuse and displaced, often functional valvular incompetence and murmurs.
- May be AF (esp. in alcoholics) and associated emboli.
- Typically, patient is male, 40–50yrs.
- HIV cardiomyopathy occurs in younger patients.

Diagnosis and management

Echocardiography usually shows a dilated hypokinetic heart with involvement of all cardiac chambers. In HIV-associated cardiomyopathy, the LV may be normal size but severely hypokinetic. Evaluation is in three stages:

- *Non-invasive clinical evaluation*: exclude reversible causes including HT, alcohol, thyrotoxicosis, infiltration (iron, amyloid, sarcoid), tachycardia-induced cardiomyopathy, DM, myocarditis, and phaeochromocytoma.
- *Invasive evaluation*: coronary angiography +/− EMB in patients with risk factors for IHD or ECG suggestive of MI or when infiltrative disorders or myocarditis are suspected.
- *Family evaluation*: if no cause found, screen first-degree relatives by ECG and echocardiography to exclude familial dilated cardiomyopathy.
- Full evaluation → aetiology in 50–75% of cases. Cause linked to prognosis; investigation important when possible. Mortality of idiopathic dilated cardiomyopathy is 40% by 5yrs.
- Patients with refractory heart failure should be considered for transplantation.

Peripartum cardiomyopathy

Dilated cardiomyopathy beginning in last month of pregnancy or <5mths postpartum, with no other history of heart failure and with no discernible cause for heart failure.

Risk factors

High parity, age, low socioeconomic status. Myocarditis found in ~50%, but mechanism unclear. Cultural practices, such as eating Na^+-rich foods in hot climates in the puerperium may have a role. The combination of ↑ circulatory demand (+/− anaemia), heat (→ peripheral vasodilatation), and high salt load might → high output cardiac failure.

Investigation and management

As for heart failure. In ~50% of cases there is irreversible cardiac dysfunction. Arrhythmias, persistently dilated heart, and systemic or pulmonary emboli mark poor prognosis. If unresolved, further pregnancies can be fatal; consider tubal ligation in patients with irreversible cardiac dysfunction beyond 6mths follow-up.

Restrictive cardiomyopathy/endomyocardial fibrosis

Due to endomyocardial stiffening, resembling constrictive pericarditis. Often due to endomyocardial fibrosis in which hypereosinophilia (possibly triggered by helminthic infection, esp. filariasis) damages the myocardium. Mural thrombus formation → a fibrotic mass. Rare causes are amyloid or carcinoid.

Clinical features

May begin with a febrile illness, facial oedema, and dyspnoea that may → death within months. Most patients are seen in chronic stage with heart failure. LV disease consists of MR (never mitral stenosis or aortic regurgitation) with a third heart sound, and progressive pulmonary HT. RV disease (usually tricuspid regurgitation) → gross ascites and ↑↑ JVP, but often minimal peripheral oedema. May be exophthalmos, central cyanosis, delayed puberty, ↓ pulse pressure, and AF. Murmurs may be audible (esp. if pericardial disease). Pericardial effusion common in endomyocardial fibrosis.

Diagnosis

CXR varies from almost normal to massive cardiac shadow (aneurysm of right atrium, or pericardial effusion). Echocardiography and Doppler show fibrosis of inflow tracts with involvement of ventricles and regurgitation of mitral and tricuspid valves. May have pericardial effusion and thrombi in the atria or ventricles.

Management

Acute treatment is supportive. If eosinophilia, look for and treat cause. In established disease, resist the temptation to drain the ascites, since it may cause the patient to lose protein. Digoxin may control ventricular rate if there is AF.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is unexplained ventricular hypertrophy (i.e. hypertrophy in absence of HT, aortic stenosis, DM, obesity, or other cause) → obstruction of the LV outflow tract in 20% of cases (i.e. hypertrophic obstructive cardiomyopathy). Over 90% of cases show autosomal dominant inheritance. Genetic counselling and screening of first-degree relatives essential.

Clinical features

Dyspnoea, angina, syncope, palpitations. May be a double impulse at apex, jerky pulse, fourth heart sound, late systolic murmur. ECG almost always abnormal, showing LV hypertrophy, Q waves, and deep T-wave inversion. ECG abnormalities precede the echocardiographic onset of cardiac hypertrophy, which manifests from adolescence onwards.

Management

β-blockers for angina and treat arrhythmias. Uncontrolled AF needs anticoagulation. Consider high-risk patients (i.e. family history of sudden death, syncope, abnormal BP response to exercise) for implantable cardioverter defibrillator.

Left atrial myxoma

Rare benign tumour, developing from atrial septum → left atrial obstruction (as in mitral stenosis), emboli, AF, fever, ↓ weight, and ↑ ESR. May be a family history. Diagnosis usually on echo.

Treatment Excision—the lesion may recur.

Renal medicine

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Vivekanand Jha

Assessing renal function

Kidneys perform excretory (metabolic waste, ingested substances), synthetic (erythropoietin, renin, vitamin D) and regulatory (water, electrolyte, and acid–base balance) functions.

Serum creatinine

Simple to measure and widely available. However, serum Cr concentration remains in the normal range until glomerular filtration rate (GFR) has ↓ by ~40%, so not a useful measure of early renal impairment.

Glomerular filtration rate

- More accurate measure of kidney function.
- Normal value 90–120mL/min/ 1.73m^2.
- Can be estimated using serum Cr-based equations (estimated GFR), e.g. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) equation (mobile app or online calculators).

Urinalysis

Gross examination

- Colour: if dark—consider bilirubin, blood, Hb, drugs (esp. rifampicin), myoglobin; milky white—chyle.
- Turbidity → suspended matter (cells, pus, phosphates, chyle, crystals).
- Specific gravity (normal range 1.005–1.030):
  - ↓ in dilute urine, diabetes insipidus, renal tubular defects.
  - ↑ in dehydration, exogenous solutes, e.g. contrast agent, SIADH.

Chemical analysis (by stick)

- pH: normally acidic (range 4.5–8.0).
- Proteinuria: ➲ Proteinuria, p. 356.
- Glucose: DM, tubular disorders (renal glycosuria).
- Ketones: diabetic ketoacidosis, starvation, pregnancy.
- Nitrites, leukocyte esterase: UTI.
- Blood: RBCs, haemoglobinuria, myoglobinuria.

Microscopy

Examination of spun sediment (spin at 2000 revolutions/min for 5min, suspend pellet in a drop and examine at 10× and 40×).

Cells

- Renal tubular epithelial cells: acute tubular injury.
- Leukocytes: UTI, nephritis, indwelling catheter, contaminated urine.
- Eosinophils: interstitial nephritis.
- RBCs: disease of urinary tract or renal parenchyma. Dysmorphic (misshapen) RBCs suggest glomerular disease.

Casts

- Hyaline: normal, concentrated urine; renal tubular injury.
- Muddy brown casts: acute tubular necrosis.
- Leukocyte cast: interstitial nephritis or pyelonephritis.
- RBC casts: glomerulonephritis (GN).

Proteinuria

Classification

- Transient: orthostatic, febrile illnesses, uncontrolled hypertension, diabetes, UTI, stress, exercise, and heart failure.
- Persistent: kidney disease marker, severity correlates with disease progression and mortality.
- Heavy (>3.5g/1.73m²/d): indicates glomerular disease.
- Low grade (<1g/d): may be seen in tubular disorders.

Assessment

Qualitative tests

- Dipsticks: good screening and follow-up tool (Table 8.1). Detects albumin, does not detect small amounts. Unable to detect light chains. Dilute urine may lead to false −ve results.
- Alternatives: heat test/sulfosalicylic acid test.

Table 8.1 Urinary albumin excretion

	24h urine albumin (mg/24h)	Spot urine albumin/Cr ratio (mg/g)	Dipstick test
Normal	8–10	<30	Nil
Microalbuminuria	30–300	30–300	Trace or 1+
Overt proteinuria	>300	>300	Trace to 3+

Haematuria

Blood in the urine always requires investigation. It may be:
- Microscopic: with ≥5 RBCs/high-power field, or
- Macroscopic: i.e. can be seen with the naked eye.

While ~50% of patients presenting with haematuria in the West have neoplastic lesions, in resource-poor regions, a large number of other diseases → bleeding from the urinary tract.

Causes

- Surgical: renal stone disease; transitional cell or squamous carcinoma (CA) of the bladder, ureter, or pelvis; renal cell CA; trauma; benign prostatic hyperplasia; arteriovenous malformations.
- Medical: UTI, schistosomiasis, TB, glomerular disease (IgA nephropathy, GN, SLE), polycystic kidneys, infarction, bleeding diatheses.

Investigating haematuria

Look for stones, malignancy, UTIs, and schistosomiasis (in endemic areas) before considering rarer medical causes. Ask the following questions:
- Is it true haematuria? Check other causes of red urine (haemoglobinuria, myoglobin, porphyrins, beetroot; Box 8.1).
- What is its timing in relation to micturition? Early haematuria → low (urethral/genital) bleeding site, late haematuria (i.e. at the end of voiding) → bladder site; red colouration throughout micturition → ureteric or renal lesion.
- Is the haematuria painful? CA and schistosomiasis tend to be pain-less, cystitis, obstruction (e.g. stones), and infection are commonly painful.
- Is there dysuria and fever (UTI), poor stream (urethral/bladder neck lesion), loin pain (ureteric obstruction due to tumour, stone, or clot), family history (polycystic kidneys), or a history of trauma?

Diagnosis

Urine microscopy (RBC casts and dysmorphic RBCs suggests glomerular bleeding), culture, cytology; USS; intravenous urogram (IVU); cystoscopy, FBC.

Box 8.1 Is it true haematuria?

Haemoglobinuria

Caused by intravascular haemolysis due to toxins/venoms, falciparum malaria, incompatible blood transfusions, G6PD deficiency, paroxysmal nocturnal haemoglobinuria, chronic cold agglutinin disease, microangiopathic haemolytic anaemia, march haemoglobinuria.

Myoglobinuria

Caused by rhabdomyolysis after muscle injury, excessive contraction (convulsions, tetanus, hyperthermia, very heavy exercise), viral myositis (influenza, Legionnaires' disease), and drugs/toxins (alcohol, snake venoms). Myoglobinuria may be idiopathic.

Chyluria

- Passage of lymph in urine → milky appearance. Sometimes seen in lymphatic filariasis, rarely from other obstructions to the thoracic duct. *Presentation*: intermittent or persistent passage of milky white urine. May be precipitated by fatty meals and associated with colic, haematuria, and fever. *Diagnosis*: microscopy for chylomicrons and assays for triglycerides in urine. Investigate site of leakage of lymph by imaging studies.
- Treatment: low-fat diet and high fluid intake; treat lymphatic filariasis; some lesions irreversible. Endourological instillation of silver nitrate or surgical repair of fistulae in refractory cases.

Imaging in renal disease

- Plain radiography: may show radio-opaque stones, calcification in renal parenchyma/collecting system, renal size/contour, and position of stents/drains.
- Excretory urography (aka IV urography): X-ray before and after injecting radiocontrast agents. May show parenchymal function, anatomy of excretory system, and excretion kinetics.
- Retrograde and antegrade pyelography: may show of urinary tract anatomy, by puncturing the kidney or endourologic route.
- Cystourethrography: for bladder volume, size, and shape. Voiding cystourethrography for lower tract anatomy, voiding function, and vesicoureteric reflux.
- Ultrasonography: for kidney size, shape, and obstruction, abscess, cysts, and mass. Doppler for vascular anatomy and perfusion and guided interventions such as biopsy, punctures, and drainage procedures.
- CT scan and MRI: high-resolution imaging of renal parenchyma, collecting system, and vasculature; may show cortical necrosis, infections, and vascular anatomy.
- Nuclear imaging: e.g. for differential renal function, outflow obstruction, and renal scars.

Kidney biopsy

A core of renal tissue obtained percutaneously with a needle, usually with US guidance. Complications—visible haematuria in <5%, usually resolves <24h. Persistent haematuria/perirenal haematoma may need intervention.

Common indications

- Renal involvement in systemic conditions—vasculitides, autoimmune disorders, haematological malignancies, plasma cell dyscrasias, granulomatous disorders, thrombotic microangiopathy.
- 1° renal disease: GN, unexplained ↓ GFR, AKI with delayed recovery or unusual features, unexplained glomerular haematuria.
- Kidney transplant recipients—graft dysfunction.
- Evaluation by light microscopy for morphological pattern of injury, immunofluorescence/immunoperoxidase for immune deposits and special antigens, and electron microscopy for ultrastructural changes.

Acute kidney injury

Defined as ↑ serum Cr by 0.3mg/dL within 2d or by 50% within 7d, or oliguria (urine output <0.5mL/kg for 6h). Pre-existing chronic kidney disease (CKD) ↑ AKI risk.

Causes of AKI

- Pre-renal (renal hypoperfusion):
  - Hypovolaemia: GI losses, haemorrhage, burns.
  - ↓ cardiac output and shock.
  - ↓ effective circulatory volume: cirrhosis, heart failure.
  - Drug-induced hypoperfusion: NSAIDs, ARBs.
- Intrarenal (ischaemic or toxic or inflammatory):
  - Glomerular: acute GN, rapidly progressive GN.
  - Acute tubulointerstitial nephritis.
  - Vascular: vasculitis, malignant hypertension, thrombotic microangiopathy, snake bite e.g Rusel's viper.
  - Toxins: drugs esp. NSAIDs, aminoglycosides, ARB, cisplatin, amphotericin B, iodinated contrast.
  - Intravascular haemolysis, rhabdomyolysis, crystalluria.
  - Sepsis.
  - Renal ischaemia.
  - Pregnancy: pre-eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome.
- Postrenal (obstructive):
  - Ureteric obstruction (bilateral or in solitary functioning kidney).
  - Bladder outlet obstruction.

Clinical features of AKI

No specific symptoms/signs; in clinical setting, have high index of suspicion and frequent monitoring of urine volume and serum Cr.

Evaluation

- Assess hydration, need for resuscitation, and extent of other organ involvement.
- Exclude obstruction clinically and by USS.
- Urinalysis: bland sediment → prerenal, active sediment (cells, cellular casts, + proteinuria) → renal parenchymal/intrarenal disease.
- Serologic tests, haematologic tests, and kidney biopsy as appropriate.

Course and prognosis

- Determined by underlying cause. Uncomplicated acute tubular necrosis recovers in 2–6wks. May have polyuria and electrolyte imbalance during recovery phase. If persistent oliguria/non-recovery after 3wks, consider acute cortical necrosis (especially after snake bite or obstetric AKI).
- Can → CKD.

Management

- Treat the cause/precipitating factors. For Russel's viper snakebite use antivenom.

- Assess hydration (JVP, skin turgor, peripheral perfusion, mucous membranes, pulmonary crepitations, peripheral oedema, heart rate, postural BP).
- Optimize fluid balance: give fluids if dehydrated.
- Catheterize for suspected lower tract obstruction. Remove catheter if anuric.
- Urgent dialysis for pulmonary oedema, K^+ >6.5mmol/L, severe uraemia, acidosis, or encephalopathy.
- Monitor/correct electrolytes. See Box 8.2 for management of hyperkalaemia.
- Record fluid input and output. Once hydration normal, limit fluids to 500mL + losses from previous days.
- Avoid nephrotoxic or K^+-sparing drugs; adjust doses of other drugs (assume GFR as <10mL/min in established AKI).
- Restrict dietary K^+.
- During polyuric recovery phase, avoid dehydration and hypokalaemia.
- Stop metformin, ACE inhibitor/ARB. No role for renal-dose dopamine.

Dialysis

- Peritoneal dialysis (PD) esp. in children, or low-resource setting.
- Haemodialysis (HD) and its variations (sustained low-efficiency dialysis, continuous renal replacement therapy).
- Repeat as needed, more frequent in hyper-catabolic patients.
- Type of dialysis does not affect outcome.

Box 8.2 Treatment of hyperkalaemia

- Urgent treatment needed if K^+ >6.5mmol/L or ECG changes (tall peaked T waves, prolonged PR interval, or broad QRS complexes).
- IV 10% calcium gluconate 10mL over 1min, repeated every 3–10min until ECG changes reverse.
- 50–100mL of 25% or 50% glucose with 10–20U of regular insulin repeated every 6–8h.
- Salbutamol nebulizer.
- Sodium bicarbonate if metabolic acidosis present (50–100mL 7.5% solution as slow infusion, can be repeated as needed).
- Cation exchange resins (calcium polystyrene sulfonate or sodium polystyrene sulfonate) 15–30g as suspension in water or sorbitol orally or as retention enema, repeat every 4–6h.
- Dialysis.

Chronic kidney disease

Definition

Significant abnormalities of kidney structure or function for >3mths. Occurs in ~10% of population. CKD is a risk factor for infections, hospitalizations, cardiovascular diseases, and cancer. Once estimated GFR <45mL/min, CKD often → end-stage renal disease (ESRD). Risk factors for progression incl. cause, GFR, albuminuria, age, male sex, race/ethnicity, hypertension, hyperglycaemia, dyslipidaemia, smoking, obesity, cardiovascular disease, exposure to nephrotoxic agents. CKD complications incl. anaemia, metabolic bone disease, wasting.

Causes

Diabetes (commonest), hypertension, GN, interstitial nephritis, obstructive nephropathy, post-AKI, polycystic kidneys, genetic or developmental and systemic diseases. Cause cannot be established in many patients. Certain areas of world have 'hotspots' with high incidence of CKD of unknown cause.

Presentation

Early stages asymptomatic. Usually detected on screening for other reasons. Later—anaemia, oedema, hypertension, breathlessness, nausea, anorexia, fatigue, pruritus, and bone pains.

Investigations

- Estimate/measure GFR, urinalysis (albuminuria, sediment abnormalities).
- Specific tests for cause as indicated.
- USS for kidney size, and anatomical abnormalities. Small <7cm kidneys diagnostic of CKD.
- Investigations to assess severity and extent of complications.

Management principles

- Prevent/treat acute insults: UTI, drugs, hypovolaemia, heart failure, urinary obstruction, nephrotoxic agents.
- BP control (<140/90mm Hg or <130/80mmHg in proteinuric states), dietary protein restriction (0.8g/kg/day), stop smoking, exercise, salt restriction, glucose control, proteinuria management, treatment of acidosis.
- ARBs: check K^+ and Cr 2–3 week after start and discontinue if Cr rise >30% or K^+ >6mEq/L.
- Anaemia: look for iron deficiency and treat. Erythropoiesis stimulating agents if Hb <9g/dL in iron-replete state.
- Manage hyperphosphataemia by diet and oral phosphate binders.
- Correct vitamin D deficiency.
- Vaccinations: follow local guidelines. Hepatitis B, pneumococcal vaccination, and influenza vaccine recommended.
- Evaluate and manage cardiovascular disease risk: tobacco cessation, exercise, weight control, BP control, and statins.
- Avoid malnutrition, treat when present.

ESRD care planning

- Shared decision-making for renal replacement therapy.
- Listing for transplant in suitable candidates, pre-emptive transplant when possible.
- Advance plan for HD or PD.
- Save veins in non-dominant arm (no venepuncture/IV line) for arteriovenous fistula construction.
- Create arteriovenous fistula once estimated GFR <15mL/min and dialysis expected in next few months.

Diabetic nephropathy

- 20–30% of diabetics develop kidney disease.
- Commonest cause of CKD worldwide.
- 30–40× risk of death vs a diabetic with no nephropathy.
- Retinopathy often coexists.
- Presents with progressive albuminuria, ↑ BP, and ↓ GFR; ~1/3 subjects can have isolated GFR loss.
- Suspect non-diabetic renal disease when retinopathy absent, short duration of diabetes, kidney disease progresses rapidly, RBC casts in urine, abrupt-onset massive proteinuria.

Specific management issues

- Target level of glycated haemoglobin (HbA1c) 7%.
- Can use metformin until GFR <45mL/min.
- BP control, preferably with ARBs.
- Comorbidities: cardiovascular disease, infections, bone disease, neuropathy, and vascular disease.

End-stage renal disease

- Irreversible loss of kidney function indicating need of renal replacement therapy (usually at GFR <5mL/min).
- Manifestations: malnutrition, failure to thrive, ↑ K^+, acidosis, volume overload, pericarditis, encephalopathy, uncontrolled nausea or vomiting, pruritus, neuropathy, and restless legs.
- Treatment: renal replacement therapy (kidney transplantation, HD, PD) or supportive (conservative) therapy.

Peritoneal dialysis

- PD catheter is placed in abdomen and instillation of 30–40mL/kg of PD fluid done at regular intervals after draining fluid instilled in previous cycle.
- Done at home, needs minimum infrastructure. Infection in abdomen (peritonitis) and dialysis failure are the main complications. Peritonitis managed by adding antibiotics to the PD fluid.
- Continuous ambulatory PD: manual PD fluid exchanges, 3–4 cycles per day each dwelling 4–6h.
- Continuous cycling PD or automated PD: using automated PD fluid exchange machines.

Haemodialysis

- Uses a dialyser cartridge; access by creating arteriovenous fistula or by wide-bore catheters placed in central veins.
- Done 2–5× a week, in centre or at home each session lasting 4h.
- Haemodynamic stress, risk of blood borne infections, and exposure to water contaminants are most important complications.

Kidney transplantation

Preferred treatment for ESRD in suitable subjects. Donor kidney (allograft) is surgically implanted in the iliac fossa. Lifelong immunosuppression needed. Initial success rates 95–98% and average graft survival 10–15yrs.

Donor source

- Living donor: healthy adult genetically/emotionally related.
- Deceased donor: brain-dead subject.

Histocompatibility

- ABO compatibility—cross blood-group transplant can be done after removing blood group antibodies.
- Immunological compatibility established by cross matching.
- HLA compatibility between donor and recipient improves long-term outcomes.

Immunosuppression

Calcineurin inhibitors (cyclosporine or tacrolimus), anti-metabolites (mycophenolate and azathioprine), and steroids. Antibodies used for induction and for treatment of rejection.

Major complications

Graft rejection (acute and chronic), surgical complications, infections, new-onset diabetes, malignancies, bone marrow suppression, and recurrence of renal disease.

Glomerular diseases

Damage to glomerular filtration barrier → leakage of protein and/or RBCs +/− ↓ in GFR. Diagnosis requires kidney biopsy. Nomenclature and classification based on light microscopy, immunofluorescence, and electron microscopy. Can be inflammatory (GN) or non-inflammatory. 1° when kidney is the main involved organ, or 2° when part of a systemic process. See Table 8.2 for major glomerular diseases, their presentation, and important causes.

Presentation

- Main clinical syndromes: acute GN (haematuria, proteinuria, oliguria, ↓ GFR, hypertension), nephrotic syndrome (proteinuria ++ and oedema), mixed nephritic–nephrotic.
- Non-inflammatory glomerulopathies present with proteinuria.
- Inflammatory GNs present with proteinuria, haematuria, hypertension, ↓ GFR, ↓ urine output, and ↑ BP.

Table 8.2 Major glomerular diseases, their presentation, and important causes

Histology	Presentation	Major 2° causes
Postinfectious GN	Acute nephritic syndrome following infection esp. sore throat	Post-streptococcal GN is commonest but can develop after many infections
Minimal change disease (MCD)	Childhood nephrotic syndrome, characterized by remissions/relapses	Allergies, drugs, infections, haematological malignancies
Membranous glomerulonephritis (MGN)	Common in adults. ~80% have antibodies to PLA2R and 5% have antibody to THSD7A. One-third can progress to ESRD over a decade	Malignancies, SLE, thyroiditis, chronic infections
Membranoproliferative GN (MPGN)	Nephrotic–nephritic presentation. Most frequent in children and young adults. ESRD in 50–60%	Chronic infections (HCV), autoimmune disease (SLE, cryoglobulinaemia, sarcoidosis), malignancies, monoclonal gammopathies, complement abnormalities
Focal segmental glomerulosclerosis (FSGS)	Nephrotic presentation, ↓ GFR. Can be caused by mutations in podocyte proteins. 50% → ESRD	Reduced renal size, reflux nephropathy, morbid obesity, HIV, and injecting drug use
IgA nephropathy	Commonest GN globally. Seen mostly in young adults. Mixed nephritic/nephrotic. ~40% develop ESRD	Infections (HIV, toxoplasmosis) malignancies, GI disorders (coeliac disease, cirrhosis, Crohn's disease) and autoimmune disorders

Evaluation

- Urinalysis incl. microscopy.
- Proteinuria quantitation (preferably in a 24h sample).
- Serum Cr, albumin, lipid profile.
- Serology: depending on clinical presentation.
- Age-appropriate evaluation of malignancy.
- Kidney biopsy.

Treatment

- Salt restriction and diuretics.
- BP control.
- Antiproteinuric therapy with angiotensin II blocking drugs.
- Statins as needed.
- Manage hypercoagulable state in severe hypoalbuminemia.
- Specific treatment guided by histology, disease severity, and cause. Steroids and immunosuppressive agents (alkylating agents, calcineurin inhibitors, mycophenolic acid) are mainstay of therapy. Use of biological agents (e.g. rituximab and eculizumab) increasing.
- Proteinuria remission → good renal outcome.

Acute glomerulonephritis

Common in LMICs esp. in children. Often postinfectious. Presentation can be asymptomatic (isolated urinary abnormalities) or as symptomatic acute nephritis (10%).

Infections associated with postinfectious GN

- Bacterial: streptococcal, staphylococcal, meningococcal, *Escherichia coli*, *Pseudomonas*, *Klebsiella*, *Salmonella*, *Brucella*, *Leptospira*, *Mycobacterium leprae*, *Rickettsia*, *Mycoplasma*.
- Viral: hepatitis, EBV, CMV, parvovirus, varicella.
- Parasitic infections: malaria, *Schistosoma*, *Toxoplasma*.
- Fungal: *Candida*, *Coccidioides*, *Histoplasma*.

Presentation

- Abrupt onset of haematuria, oliguria, hypertension, ↑ Cr, and proteinuria ~7–21d after infection.
- Can → hypertensive encephalopathy, pulmonary oedema, need dialysis, and rarely rapidly progressive crescentic nephritis.

Evaluation

- Urinalysis: look for RBC casts, and dysmorphic RBCs. Proteinuria usually mild/moderate.
- If throat or skin lesion culture for group A streptococci.
- Serum antistreptolysin O and anti-DNAase B, complement levels.
- Blood count and renal function.

Treatment

- Supportive.
- Salt and water restriction if oedema/fluid overload.
- Diuresis as needed.
- Treat complications (hyperkalaemia, acidosis).
- BP control.
- Dialysis as needed.
- Treatment of residual streptococcal infection (does not alter the course of illness): penicillin or macrolide antibiotic.

Outcome

- Usually resolves spontaneously in 2–4wks.
- Microscopic urinary changes may persist for few months.
- May develop progressive CKD.

Renal involvement in systemic diseases

Causes

- Autoimmune: SLE, antiphospholipid syndrome, connective tissue diseases, e.g. mixed connective tissue disease, rheumatoid arthritis, Sjögren's syndrome.
- Vasculitides.
- DM.
- Amyloidosis.
- Sarcoidosis.
- Chronic liver disease (hepatorenal syndrome and IgA nephropathy).
- Sickle cell nephropathy: pain, haematuria, papillary necrosis, nephrotic syndrome, renal infarction, tubular disorders, and medullary cancer.
- Lipodystrophy.
- Infection-associated GN.

Urinary schistosomiasis (bilharzia)

Caused by *Schistosoma haematobium* in Africa and parts of the Middle East. *S. intercalatum* and hybrid species can produce atypical clinical pictures, with ectopic localization of worms. For distribution and life cycle, see ➲ Schistosomiasis (bilharzia), p. 264. Worm eggs → a T-cell-mediated immune response → eosinophilic granulomata in the bladder, uterus, and genitals. Eggs may also affect the GI tract, lungs, liver, skin, and CNS.

Transmission

Requires:

- Human (definitive host) availability and freshwater contact.
- *Bulinus* snails (intermediate host).
- S. *haematobium*.

Peak prevalence 15–30yrs, then ↓ due to age-related changes in water-contact, ↑ immunity, and death of adult worms.

Clinical features

- Egg deposition: begins 3mths after infection → painless haematuria, which may persist for months or years, +/– dysuria, pain, malaise, and mild fever.
- Established infection: haematuria often ↓ in chronic stage, unless there is infection, ulceration, or malignancy. Fibrosis and calcification of bladder → ↓ volume → frequency and dribbling. Other complications include perineal fistulae and bacterial infection. In severe cases → urinary retention, stasis, stone formation, and renal failure. In men, involvement of seminal vesicles → eggs shed in semen ('lumpy' semen); prostate, epididymis, and penis uncommonly affected. In women, ulcerating, polypoid, or nodular lesions may be seen in the vulva, vagina, and cervix. The ovaries, fallopian tubes, and uterus rarely affected. *S. haematobium* infection may → ectopic pregnancies and infertility. Heavy/lifelong infection predisposes to squamous bladder CA.

Diagnosis

- Microscopy: parasite eggs in urinary sediment, bladder biopsies, or rectal mucosal snips. Schistosome ova large (150 × 50μm); require low-power only (➲ Colour plate 7). Distinguish viable ova by flickering 'flame cell' visible in wet preparation, by observing eggs hatching in water, or by being uncalcified with intact organelles in biopsies.
- Serology: antibodies to *Schistosoma* develop 6–12wks post exposure.
- Imaging: USS → bladder wall thickening or hydronephrosis. Heavy infections may → bladder calcification on AXR ('fetal head' sign); IVU may show hydronephrosis, hydroureter.

Treatment

See ➲ Schistosomiasis (bilharzia), p. 264. Praziquantel is effective against all species of schistosomes; dose of 40–60mg/kg oral given in divided doses over 1d usually curative. Follow-up at 2 and 6mths for urinalysis and clinical assessment. If in doubt, do cystoscopy to exclude bladder CA.

Box 8.3 *Schistosoma haematobium* and bladder cancer

Association between bladder CA and chronic heavy *S. haematobium* infection well recognized. Lag period of >20yrs between infection and development of CA. 75% of patients (with squamous bladder CA) in Egypt are <50yrs; by contrast, in non-schistosome areas, most patients (with adenocarcinoma) are >65yrs. ↑ Common in males, smokers, and those working with aromatic amines (e.g. in the rubber industry).

Clinical features

Haematuria, cystitis, and obstruction. Spread is local → pelvic structures, via the lymphatics → iliac and para-aortic nodes, and via the blood → liver and lungs.

Investigation

Urinalysis, FBC. AXR may show a calcified bladder wall. Perform IVU, cystoscopy, and biopsy.

Management

Cystoscopic diathermy for superficial tumours. Intravesicular chemotherapy or BCG administration, radical surgery, and radiotherapy or palliation (long-term catheterization) depending on stage.

Infections and kidney disease

Infections can → kidney disease by direct invasion, immune activation, cytokine release, or volume depletion (Table 8.3).

Malaria

Acute kidney injury

- Can be seen with *Plasmodium falciparum, P. knowlesi*, and *P. vivax*. Common in Africa and S and SE Asia. Non-immune subjects ↑ vulnerability. Due to multiorgan dysfunction, direct involvement of renal microcirculation, and immune effects. Presentation with oliguric AKI, hyperbilirubinaemia, thrombocytopenia, and DIC. Mortality 15–50%. *Treatment:* artesunate as for severe malaria.

Malarial glomerulopathies

- Quartan malarial nephropathy—rare nowadays. In sub-Saharan Africa, caused by *P. malariae*, presenting as nephrotic illness in children 5–8yrs.
- Acute GN with *P. falciparum* and *P. vivax*—mild proteinuria, microscopic haematuria, and casts, usually self-resolving.

Leishmaniasis

Infection with the intracellular parasite *Leishmania donovani* can → proteinuria, haematuria, acute nephritis, nephrotic syndrome, or tubular dysfunction.

Hepatitis B and C

Can → immune complex-mediated GN. Presentations range from asymptomatic urinary findings to nephrotic/nephritic syndrome and rapidly progressive renal failure. *Treatment*: antiviral drugs, rituximab for severe cryoglobulinemia/vasculitis.

HIV

Can → AKI and/or CKD 2° to direct infection or indirect effect of infection and/or treatment. *Treatment*: ART.

Mycobacterium tuberculosis

- Can directly infect the urinary tract → sterile pyuria, haematuria, dysuria, frequency, and constitutional symptoms.
- Ureteric strictures, and bladder fibrosis → obstructive uropathy.
- Renal manifestations: destructive necrosis → to putty kidney, granulomatous interstitial nephritis, and amyloidosis.
- Diagnosis by imaging, demonstration of mycobacteria in early morning specimens of urine or biopsy.
- *Treatment* with standard anti-TB chemotherapy.

Hantavirus

AKI as part of haemorrhagic fever with renal syndrome. *Treatment* is supportive.

Dengue

Mosquito-borne viral disease, presents with constitutional symptoms, thrombocytopenia, and capillary leak. Renal manifestations: proteinuria, haematuria, tubular injury, and HUS. *Treatment*: supportive.

Yellow fever

Mosquito-borne disease can cause AKI as part of severe multisystem involvement and sepsis syndrome. *Treatment*: supportive.

Leptospirosis

Spirochaetal infection, presents with mild febrile illness to severe multisystem (Weil's) disease. AKI due to tubulointerstitial nephritis, liver failure, and pulmonary haemorrhage. Tubular function abnormalities cause acidosis, hypokalaemia, and hypomagnesaemia. Treatment with penicillin, ceftriaxone, cefotaxime, macrolides, or doxycycline.

Scrub typhus

Caused by rickettsial organism *Orientia tsugatsugamushi*. Presentation with acute febrile illness and AKI. Diagnosis by serology and/or PCR. *Treatment*: doxycycline.

Table 8.3 Common differential diagnosis of acute febrile illness associated with AKI in tropics

Clinical picture	Differential diagnosis
Fever + jaundice	Leptospirosis, malaria, dengue, hantavirus, rickettsiosis, acute hepatitis
Fever + conjunctival suffusion + thrombocytopenia + ↑ liver enzymes	Leptospirosis
Continuous fever + severe respiratory symptoms leading to ARDS	Hantavirus
Fever + severe myalgia + thrombocytopenia	Dengue
Fever + maculopapular rash + 'eschar'	Scrub typhus
Fever + splenomegaly + thrombocytopenia	Malaria
Fever + exposure to unpasteurized milk products	Brucellosis

Rapidly progressive glomerulonephritis

Characterized by rapid ↓ GFR over days–weeks, with features of GN. Renal histology shows crescents (proliferation of parietal epithelial cells). Can have associated involvement of other organs, and have a relapsing course.

Categories

- Immune complex mediated: idiopathic, or on background of a primary GN (MPGN, IgA nephropathy, PSGN) or systemic disease (lupus, Henoch–Schönlein purpura, cryoglobulinemia).
- Pauci-immune: no or scarce immune complexes in glomeruli. Most cases antineutrophil cytoplasmic antibody (ANCA) +ve, i.e. part of systemic vasculitis.
- Anti-glomerular basement membrane (GBM) antibody mediated: renal limited or pulmonary–renal (Goodpasture's) syndrome.
- Idiopathic.

Evaluation

- Kidney function tests, FBC, and urinalysis.
- Serology: ANCA, anti-GBM antibody, antinuclear antibodies, complement and as directed by clinical evidence.
- Kidney biopsy.

Treatment

- Supportive treatment.
- Immunosuppression: steroids, cytotoxic drugs (cyclophosphamide, mycophenolate), plasmapheresis for vasculitis (especially if dialysis dependent), and anti-GBM antibody-mediated disease (when non-dialysis dependent).
- Aggressive initial management and long-term maintenance.

Tubulointerstitial disease

Acute tubulointerstitial nephritis

Causes

- Drugs: beta-lactams, rifampicin, quinolones, macrolides, NSAIDS, allopurinol, PPI, etc.
- Infections: *Streptococcus*, *Pneumococcus*, *Legionella*, *Campylobacter*, *Salmonella, Leptospira, Toxoplasma*, CMV, hepatitis, mumps, polyomaviruses.
- Connective tissue disorders (e.g. Sjögren's syndrome, SLE, sarcoidosis).

Presentation ranges from mild asymptomatic disease to severe AKI. Most patients recover if treated promptly, residual kidney disease if treatment delayed.

Evaluation

- Detailed history is key.
- Urine exam: low-grade proteinuria, WBC, WBC casts. Eosinophilia characteristic but uncommon, requires special stains.
- Ultrasonography: normal sized or enlarged kidneys.
- Kidney biopsy: confirmatory.

Treatment and outcome

- Stop offending drug, treat underlying disorder when present.
- Short course of steroids hastens recovery and ↓ long-term sequelae.

Chronic tubulointerstitial nephritis

Characterized by slowly progressive interstitial inflammation, fibrosis, and tubular atrophy.

Causes

- Drugs: NSAIDs, calcineurin inhibitors, lithium, antiviral drugs (nucleoside inhibitors), antineoplastic drugs, e.g. cisplatin.
- Infections: pyogenic infections, TB.
- Immune mediated: Sjögren's syndrome, SLE, sarcoidosis.
- Heavy metals: lead, mercury, cadmium.
- Urinary tract obstruction.
- Others: haematological malignancies, amyloidosis, myeloma, sickle cell disease; Balkan endemic nephropathy; Chinese herb nephropathy; idiopathic; and CKD of uncertain origin.

Presentation

Insidious ↓ GFR, often asymptomatic. Low-grade proteinuria, polyuria, nocturia, electrolyte disturbance, acidosis, anaemia, bone disease. May present with advanced renal failure.

Management

- Identify and treat the cause.
- Correction on hydration, electrolytes, acidosis, anaemia, and bone disorder.

Urinary tract infection

Common in women, diabetics, malnourished people, and immunosuppressed individuals. ↑ Risk with indwelling catheters or abnormalities of urinary tract. Usually begins with lower urinary tract (urethritis, cystitis) → ascends to upper tract → pyelonephritis.

Clinical features

- Cystitis: dysuria, frequency, urgency, haematuria, and pyuria. Fever usually mild. Common in sexually active women, or men with prostatomegaly.
- Pyelonephritis: lower urinary symptoms followed by high fever, chills/rigors, constant renal angle pain, tenderness, and occasionally AKI. Complications: renal/peri-renal abscess, pyonephrosis, emphysematous pyelonephritis (in diabetics).
- Abscesses, pyonephrosis: symptoms and signs of UTI fail to resolve on standard therapy; renal tenderness++; fullness in contour over renal angle; progressive sepsis and typical imaging findings.

Assessment

- Urine dipstick: for bacteria and WBC.
- Microscopy: pyuria, WBC casts = pyelonephritis.
- Urine culture: collect clean catch mid-stream sample.
- Blood culture (for severe forms), FBC, and renal function tests.
- USS and/or CT scan for evaluation of obstruction, pyelonephritis, renal and peri-renal abscess.

Management

- Uncomplicated UTI: hydration and short-course oral antibiotic covering the Gram −ve pathogens as per local profile (e.g. trimethoprim, co-amoxiclav, fluoroquinolone, cephalosporin, or nitrofurantoin for 3–5d).
- Pyelonephritis: managed in hospital with IV antibiotics until afebrile. Can switch to oral according to sensitivity. Optimal duration: 2–3wks.
- Abscess, complicated pyelonephritis: need longer duration of therapy. Percutaneous, endoscopic, or surgical intervention may be needed to drain pus or remove obstruction.
- Recurrent UTI: exclude structural/functional causes. Gynaecological examination for local cause. Improved hygiene, double void, and suppressive antibiotic for 6wks to 6mths. In postmenopausal women consider topical oestrogen cream to urethra/vulva. Treat breakthrough infection promptly.
- Catheter-associated UTI: no treatment needed if asymptomatic. With symptoms, replace catheter under single-dose aminoglycoside cover and treat as cystitis for 7d.
- Asymptomatic bacteriuria: $>10^5$ colony count of bacteria in urine culture with no symptoms. Treatment only in pregnancy or before surgical interventions in urinary tract.

Vesicoureteral reflux

Retrograde movement of urine from the bladder into the upper urinary tract due to incompetent ureterovesical junction.

- Can be 1°, or 2° to high pressure from bladder outlet obstruction.
- Common urological anomaly in children; genetic predisposition.
- Resolves spontaneously in most by age 2yrs.

Presentation

- Detection *in utero* during fetal USS.
- Childhood and/or recurrent UTI, hypertension, 2° FSGS, progressive CKD.

Diagnosis

Voiding cystourethrogram, radionuclide (DMSA) scan.

Management

- Prompt treatment of UTI.
- Long-term suppressive antibiotic treatment (trimethoprim, trimethoprim–sulfamethoxazole, or nitrofurantoin)—continued until adolescence or until reflux resolves or is corrected.
- Severe reflux or failure of medical therapy: endoscopic or open surgery.
- Regular assessment of growth, BP, and kidney function.

Renal stones

Crystallization in urine affected by diet, BMI, fluid intake, and predisposing conditions (malabsorption syndrome, bariatric surgery, immobilization, 1° hyperparathyroidism, renal tubular acidosis, UTI, etc.). Common stones are calcium oxalate (75%), and may be recurrent in ~50% of cases.

Presentation

Asymptomatic, or colicky pain in loin or flank → lower abdomen or genitals. Often associated with vomiting or haematuria. Ureteric obstruction → hydronephrosis. Stones or gravel may be passed in urine.

Evaluation

- Plain radiograph for radio-opaque stones (90%).
- US or CT scan.
- Stone analysis.
- Recurrent stone formers may need metabolic work up: serum PTH and excretion of calcium, phosphate urate, oxalate, pH, Na^+, and K^+.

Management

- Pain management: NSAIDs or opiates.
- ↑ water intake >2.5–3L/d.
- Alkalization of urine if uric acid stones.
- Salt restriction if calcium stones.
- <5mm stones pass spontaneously; 5–10mm stones often (50–70%) pass with hydration, NSAID, and alpha-blocking agent.
- Interventions needed for stone >10mm in size, failure of medical therapy, severe uncontrolled pain, upstream infection, or staghorn calculi.
- Non-surgical options—extracorporeal shockwaves lithotripsy or endoscopic (percutaneous or endourological) removal.
- Open surgery needed occasionally.
- Management of underlying metabolic abnormalities.

Kidney disease in pregnancy

Kidney disease ↓ fertility as well as fetal and maternal outcomes. Pre-existent kidney disease ↑ risk of pre-eclampsia, severe pre-eclampsia, ↑ proteinuria, ↑ progression of kidney disease, fetal loss, and growth retardation. Lupus nephritis can worsen.

Physiological changes during pregnancy

- Hydronephrosis: very common and more on right side, due to uterine compression and ovarian vein crossing the ureter.
- ↑ GFR (up to 50%), → ↓ serum Cr and uric acid.
- Mild proteinuria (up to 300mg/d).

UTI

Develops in 20% of pregnancies, ↑ risk of pyelonephritis. Screening and treatment of asymptomatic bacteriuria recommended.

Specific kidney diseases in pregnancy

- Pre-eclampsia-eclampsia: new-onset hypertension (>140/90mmHg), proteinuria (>300mg/d) after 20wks' gestation. Resolves after delivery. *Management*: antihypertensive drugs suitable for use in pregnancy. Injectable magnesium sulfate helpful for severe pre-eclampsia. ↑ lifetime risk of hypertension and ESRD.
- HELLP syndrome: variant of severe pre-eclampsia with consumptive coagulopathy and microangiopathy. Prompt delivery and supportive management required.
- Acute cortical necrosis: can develop as a complication following severe ante-or postpartum haemorrhage and microvascular disease including HUS. Presents with anuria, AKI may be irreversible.
- Acute fatty liver of pregnancy: seen in late pregnancy. AKI common and severe. *Treatment*: prompt delivery.
- Hyperemesis gravidarum can induce AKI due to volume loss.

Renal artery stenosis

Narrowing of one or both renal arteries, important cause of 2° hypertension or kidney failure. Can be caused by:

- Fibromuscular disease, esp. in young females.
- Atherovascular disease, usually with generalized atherosclerosis.
- Takayasu arteritis: esp. in South Asia; involvement of aorta and large branches.

Presentation

Hypertension, flash pulmonary oedema; bilateral disease may → ↓ GFR, esp. after starting ARBs. Absent peripheral pulses and constitutional symptoms in Takayasu arteritis.

Evaluation

Examination may show renal artery bruit and asymmetric peripheral pulses. USS may show ↓ kidney size. Imaging (Doppler, CT, MRI, or digital subtraction angiography) needed to define the lesion.

Management

BP control, atherovascular risk management, careful use of ARBs.

Intervention

- Young with fibromuscular disease/Takayasu arteritis: angioplasty.
- Atherosclerotic disease: endovascular revascularization only in selected cases for resistant hypertension, rapidly ↓ GFR, or flash pulmonary oedema.

Renal mass

Differential diagnoses of enlarged kidneys/renal masses include infections, cysts, tumours, or hydronephrosis. ~80% of all solid renal masses are malignant. Enlarged kidneys tend to bulge forwards, while perinephric abscesses or collections tend to bulge backwards. With chronic obstructed states and tumours, mass is usually better defined and less tender. Bilateral, irregular kidneys suggest polycystic renal disease.

Types of renal tumours

- Renal cell carcinoma: commonest in men and age >65yrs. Occasionally multicentric and rarely bilateral.
- Benign tumours: usually <4cm; oncocytoma and angiomyolipoma commonest and have specific imaging features.
- Urothelial tumours: arise from renal pelvis and urinary tract; commonest histology is transitional cell carcinoma.
- Wilms tumour: undifferentiated mesodermal tumour, malignant and almost exclusively seen in childhood. Can be familial.
- Metastatic deposits or diffuse renal infiltrations.

Presentation

Detected incidentally on imaging, loin pain, mass, haematuria, fever, constitutional symptoms, new-onset varicocele, or polycythaemia.

Diagnosis

- USS: complex cysts and solid renal mass.
- Confirmation by CT scan, MRI, or positron emission tomography scan.
- FNAC or biopsy helpful for smaller lesions being contemplated for non-surgical management.

Treatment of renal cell carcinoma

- Partial or radical nephrectomy. 5yr survival for localized renal cell CA 95%, falls to 12% with metastatic disease.
- Cryoablation or radiofrequency ablation for small localized tumours.
- Advanced renal cell CA : cytoreductive surgery, immunotherapy, antiangiogenic therapy and palliative radiotherapy.

Inherited renal disease

Commonest cause of CKD in children. Family history may or may not be present.

Cystic diseases

Genetic mutations in proteins of the ciliary compartment of cell membrane → bilateral multiple renal cysts and progressive CKD.

- Autosomal dominant polycystic kidney disease (ADPKD):
  - Commonest genetic kidney disease. Presents with large kidneys riddled with fluid-filled cysts. ESRD in a majority (4th–8th decade). Presentation: hypertension, progressive CKD, pain, bleeding, infection. Extrarenal features: liver cysts, intracranial aneurysms.
  - Tuberous sclerosis complex: multisystem hamartoma and renal angiomyolipomas.
  - Von Hippel–Lindau disease: retinal and CNS hemangioblastoma, pheochromocytoma, and pancreatic cysts.
  - Medullary cystic disease.
- Autosomal recessive polycystic kidney disease (ARPKD):
  - Detected on fetal or neonatal USS, biliary ectasia, liver fibrosis. Nephronophthisis.
- X-linked:
  - Orofacial digital syndrome type 1: oral frenula, cleft tongue, cleft palate, digital anomalies. Diagnosis by clinical picture, family history, and imaging. Management: supportive and general management of CKD; screening for renal and extrarenal complications; vasopressin-2 receptor antagonist for selected cases of ADPKD; genetic counselling.

Glomerular basement membrane disorders

Alport syndrome, thin basement membrane nephropathy, and nail–patella syndrome: no specific therapy available.

Chapter 9

Neurology

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Impaired consciousness

Patterns of arousal and awareness are complex and variable, and range from full consciousness to coma. Although various terms have been applied to these intermediate states, overlap inevitably occurs.

Acute confusional state and delirium

Clinical features

May fluctuate and include:

- Globally impaired cognition and clouding of consciousness.
- Short attention span.
- Easy distractability.
- Disorientation in time and place.
- Bewilderment.
- Impaired recall and memory.

Delirium More florid and may be accompanied by frightening hallucinations and/or delusions, irritability, and/or aggressive behaviour.

Check carefully

For signs of ↓ consciousness, particularly drowsiness. This may be a warning of impending coma. Psychiatric causes of confusion (e.g. schizophrenia, paranoia) and early dementia do not cause drowsiness.

Management

- If possible, identify and treat cause (Box 9.1). Common causes vary with age and geography. Look carefully for focal infection (incl. chest, urinary tract, surgical wounds, IV cannula sites, CSF).
- Give 50mL of 20% glucose IV if hypoglycaemia suspected.
- At night, turn the lights on to improve the patient's orientation.
- Treat disturbed behaviour with chlorpromazine (25–50mg IM/po tds) or haloperidol (0.5–3mg po tds; or 2–10mg IM, repeated as necessary every 4–8h to a maximum daily dose of 18mg).
- Avoid benzodiazepines as they may worsen confusion.

Nursing is very important If possible, use a well-lit room with familiar staff. Attempt to reassure the patient.

Coma

Coma is a state of unresponsiveness in which the patient lies with eyes closed and cannot be aroused to respond appropriately to stimuli. Coma is usually defined as a GCS score of ≤8 (Box 9.2). The three broad categories of coma and common associated signs are:

- *Metabolic*: normal pupil responses; normal or absent eye movements (depending on the depth of coma); suppressed, Cheyne–Stokes, or ketotic respiration—drug overdoses often → suppressed respiration; symmetrical limb signs, usually hypotonic.
- *Intrinsic brainstem disease*: from the outset there may be abnormal pupil responses and eye movements; abnormal respiratory pattern; bilateral long tract and cranial nerve signs.
- *Extrinsic brainstem disease*: *due to compression*: papilloedema and hemiparesis *with progressive* loss of pupillary responses, loss of eye movements, abnormal respiratory pattern, long tract signs.

Box 9.1 Common causes of acute confusion/delirium at presentation (they may all progress to coma)

- *CNS infection*: malaria, meningitis including TBM, encephalitis; HIV related.
- *Systemic infections*: with or without focal signs of infection.
- *Electrolyte disturbances*: ↑ Na^+, ↓ Na^+.
- *Respiratory failure*: ↓ PaO_2, ↑ $PaCO_2$.
- *Other metabolic causes*: e.g. ↓ or ↑ glucose, uraemia, hepatic encephalopathy.
- *Nutritional*: Wernicke's encephalopathy.
- *Toxins*: carbon monoxide, methanol, poisons, lead, cyanide, thallium.
- *Alcohol*: excess or withdrawal.
- *Drugs*: e.g. steroids, efavirenz.
- Head injury/concussion.
- Stroke (➔ Stroke, p. 412).
- ↑ ICP (➔ Raised intracranial pressure, p. 390).
- Epilepsy (postictal) (➔ Epilepsy, p. 425).
- Chronic subdural haematoma (➔ Subdural haemorrhage, p. 420).
- Urinary retention (esp. in elderly).

Management of the unconscious patient

Initial assessment

- ABC: ensure adequate airway, oxygenation, breathing, and circulation. Check for life-threatening injuries.
- Obtain a reliable history from witnesses: how rapidly did the patient become unconscious? Sudden onset suggests vascular aetiology, hypoglycaemia, etc. Progression to coma over days suggests, e.g. CNS infection; progression over weeks suggests, e.g. space-occupying lesion (SOL). Any relevant past medical history, e.g. diabetes, alcohol abuse, or drug overdose?
- *General exam including*:
  - Temperature (?fever/hypothermia).
  - BP (hypertension may be due to stroke).
  - O_2 saturation and respiration.
  - Neck stiffness (meningitis or subarachnoid haemorrhage (SAH), ➔ Subarachnoid haemorrhage, p. 420).
  - Signs of head injury (if suspicious, immobilize cervical spine; blood in external auditory meatus, from nose or over mastoid area, is sign of base-of-skull fracture).
  - Signs of liver or renal disease including venepuncture marks (IV drug addict might have septicaemia, brain abscess).
  - Haemodialysis shunt.
- Check blood glucose.
- Assess level of coma: use GCS or BCS (Boxes 9.2 and 9.3). Check corneal and brainstem reflexes, Doll's eye movements. Do caloric tests if brain death is suspected. Before assessing level of consciousness: exclude generalised paralysis caused by toxins (snakebite, paralytic shellfish poisoning) or drugs (e.g. barbiturates).

- *Check pupillary light reflex*:
  - Unilateral, fixed, dilated pupil suggests IIIrd nerve compression due to uncus herniation or posterior communicating aneurysm.
  - Bilateral, fixed, dilated pupils suggest brainstem pathology (herniation, massive overdoses of atropine).
  - Bilateral small pupils suggest opioid overdose, pontine haemorrhage, or organophosphate poisoning.
- *Fundoscopy*: for retinopathy (hypertensive, diabetic) and papilloedema.
- *Look for focal neurological signs*: search for asymmetry, e.g. in response to pain or in the face during expiration. If response to pain is asymmetrical, the side with ↓ response is the abnormal side (e.g. hemiparesis).
- *Identify coma due to brainstem compression*: since urgent surgery might be required. Progressive deterioration +/– focal neurology suggests possible brainstem compression.

Investigations

Depend on clinical picture and include Hb, WBC, U&E, glucose, Ca^{2+}, Mg^{2+}, LFT, TFTs, PT, ABG; blood cultures if febrile; LP if intracranial infection suspected. (Beware ↑ ICP); malaria test if potential malaria exposure; toxicology screen if overdose/poisoning suspected; skull X-ray if trauma; ECG; CXR; CT/MRI head if indicated and available.

Determine the cause and treat

- *Urgent neurosurgery and/or management of ↑ ICP* (➲ Raised intracranial pressure, p. 390): may be required for coma with focal signs, e.g. due to subdural or extradural haematoma or SOL.
- *Treat hypoglycaemia*: 50mL of 20% glucose IV; give thiamine 100mg IV before glucose if history of alcohol abuse or severely malnourished.
- *Manage suspected serious infection*: e.g. cerebral malaria (➲ Severe malaria, p. 43), meningitis (➲ Acute bacterial meningitis, p. 392).
- *Treat suspected poisoning*: see ➲ Poisoning and envenoming, p. 813.

Ongoing care

Nurse comatose patients in the ICU or high dependency unit. Monitor every 15min to 4h depending on clinical state, including vital signs; level of consciousness (GCS or BCS); pupil size, equality, and response to light. Pay special attention to respiration, circulation, skin, bladder, and bowels.

Prognosis

Depends mainly on cause, depth, and duration of coma. The combination of absent pupillary light reflex and corneal and brainstem reflexes at 24h, or the persistence of deep coma for >72h, indicate a grave prognosis.

Box 9.2 Glasgow Coma Scale

Use GCS for adults and children who are able to talk (usually >5yrs). Assess on admission and then at regular intervals to follow progress and predict prognosis.

Best motor response

- 6 Carries out request (obeys a command).
- 5 Localizes pain.
- 4 Withdraws limb in response to pain.
- 3 Flexes limb in response to pain.
- 2 Extends limb in response to pain.
- 1 Does not respond to pain.

Best verbal response

- 5 Orientated in time and place.
- 4 Responds with confused but understandable speech.
- 3 Spontaneous speech but inappropriate and not responsive.
- 2 Speech but incomprehensible.
- 1 No speech.

Eye opening

- 4 Opens eyes spontaneously.
- 3 Opens eyes in response to speech.
- 2 Opens eyes in response to pain.
- 1 Does not open eyes.

Box 9.3 Blantyre Coma Scale

The BCS is a modification of the GCS for use with children too young to talk. A score of 2 indicates 'unrousable coma'. The maximum score is 5.

Best motor response

- 2 Localizes pain.
- 1 Withdraws limb from pain.
- 0 No response or inappropriate response.

Best verbal response

- 2 Cries appropriately to pain.
- 1 Moans or abnormal cry to pain.
- 0 No vocal response to pain.

Best eye movement

- 1 Watches or follows.
- 0 Fails to watch or follow.

Headache

Brain parenchyma is insensitive to pain. Headaches result from distension, traction, or inflammation of the cerebral blood vessels and dura mater. Pain is referred from the anterior and middle cranial fossae to the forehead and eye via the Vth nerve, and from the posterior fossa and upper cervical spine to the occiput and neck via C2–3 nerve roots. Both infratentorial and supratentorial masses can → frontal headaches by causing hydrocephalus.

Causes of a headache

Primary headache

1° headache is likely in patients with a long history of similar attacks, free of symptoms between attacks, otherwise well, and no sinister symptoms or clinical signs. Three most common causes of 1° headache are:

- *Migraine*: headaches that occur at intervals (not daily) associated with N&V, anorexia, photophobia, phonophobia, and in 20% of cases, visual, mood, sensory, or motor disturbances. Most first attacks occur while young; often a family history. Identify and avoid precipitating factors; give analgesia (paracetamol, NSAIDs, or codeine) plus metoclopramide 10mg (avoid in children; dose 5mg in adolescents aged 15–19yrs). If simple analgesia inadequate, use a $5HT_1$-receptor antagonist ('triptan'). Ergotamine seldom used, because of side effects. Chemoprophylaxis (propranolol, etc.) may work for regular migraines.
- *Tension headache*: most common cause of headache. Normally a benign symptom due to an identifiable cause (e.g. overwork, family stress, lack of sleep, emotional crisis). Often a daily occurrence unlike migraine headache, getting worse as the day goes on. Visual disturbances, vomiting, and photophobia do not occur. Management involves thorough examination and reassurance of its benign course, analgesia (usually paracetamol 1g qds), and rest. Ask about drugs, caffeine, and alcohol. Amitriptyline starting at 10mg at night, increasing by 10mg each week up to 75mg, is often of benefit. Tension headaches may be part of depression—check for other signs or symptoms such as mood change, ↓ appetite, ↓ weight, ↓ libido, or disturbed sleep pattern.
- *Cluster headaches*: very severe orbital/supraorbital/temporal headaches that are strictly unilateral, usually last ~1h associated with ipsilateral eye or nasal symptoms, and may recur every other day up to many times a day. Nocturnal attacks are common. Diagnostic criteria have been proposed (see International Headache Classification, http://ihs-classification.org/en). Oxygen, triptans, and verapamil are the treatments of choice.

Secondary headache

In 2° headache, headache is the sign of a disease. Need to identify any warning features in the history.

- *SAH* (➔ Subarachnoid haemorrhage, p. 420): acute thunderclap headache (intense headache with abrupt onset). CT scan without contrast can detect recent bleeds. LP should be performed to look for xanthochromia if SAH is suspected and if the results of CT are inconclusive.

- *Giant cell arteritis (temporal arteritis)*: more common in women, mean age of onset ~70yrs. Presents with fever, tender engorged occipital or temporal artery, +/– bruits. Blindness may occur rapidly due to ischaemic optic neuropathy so diagnosis is a medical emergency. ESR markedly ↑. Temporal artery biopsy may confirm diagnosis, but do not delay treatment while awaiting biopsy. Start prednisolone 40–60mg od oral as soon as diagnosis suspected; consider higher dose, e.g. 80mg/kg or 1mg/kg in complicated cases with visual symptoms.
- *Intracranial neoplasm*: headache with symptoms of ↑ ICP (➲ Raised intracranial pressure, p. 390). Progressive neurological deficit (progressive weakness, sensory loss, ataxia) correlated with the location of the tumour. CT scan can detect most tumours, but MRI is even more sensitive as it can detect both infiltrating and very small tumours.
- *Intracranial infection (meningitis or encephalitis)*: caused by bacteria, viruses, fungi: headache with fever, +/– signs of meningism, vomiting, ↓ consciousness. LP aids diagnosis, including aetiology of the infection.
- *Analgesic-overuse headache*: also called analgesia rebound headache and chronic daily headache; follows long-term inappropriate use of analgesia. History reveals increasing and frequent use of multiple analgesics, especially codeine. *Management*—reassurance followed by stopping all forms of analgesia; may benefit from amitriptyline as above-mentioned. The headache initially worsens before improving.
- *Acute glaucoma* (➲ Acute glaucoma, p. 529): ocular emergency. Symptoms include sudden eye pain, seeing halos around lights, red eye, nausea, vomiting, sudden ↓ vision. Very high intraocular pressure (>30mmHg).
- *Sinusitis*: causes pressure-like pain +/– tenderness in a specific area of face or head, worse in the morning and exacerbated by sudden head movements, bending forwards, and sudden temperature change. *Causes*—viral and/or bacterial URTI; allergy.

Neuralgias

- *Trigeminal neuralgia*: characterized by paroxysmal attack of (usually unilateral) facial pain—intense, sharp, stabbing, or like an electric-shock, and lasting from a few seconds to several minutes/hours. May be spontaneous or triggered, e.g. by eating, talking, shaving or touch (trigger zones). Most cases believed to be caused by compression of the Vth nerve root by blood vessels; CT/MRI imaging may demonstrate cause. Carbamazepine and gabapentin are first line for relieving pain. Carbamazepine should be tried initially and dose ↑ gradually to achieve pain control. Other treatments include antidepressants, muscle relaxants, and pharmacological nerve blockade. Surgery may be indicated in patients who have failed medical therapy.
- *Post-herpetic neuralgia*: may occur as a complication of herpes zoster (➲ Varicella zoster virus, p. 565). Uncommon in young patients, but common in older age (up to 50% of patients >50yrs). Similar shooting pain to trigeminal neuralgia. Treatment includes amitriptyline, gabapentin, and topical capsaicin. Prompt treatment of herpes zoster with antivirals (and possibly amitriptyline) ↓ risk of post-herpetic neuralgia.

Raised intracranial pressure

Clinical features

- *Headache*: often worse in the morning due to CO_2 retention during sleep → cerebrovascular dilatation, possibly waking the patient from sleep; made worse by coughing, straining, standing up; relieved by paracetamol in the early stages.
- *Vomiting*: may relieve headache; sometimes first sign of ↑ ICP.
- *Altered level of consciousness*: drowsiness → coma.
- *Hypertension, bradycardia, irregular respiration*: Cushing's reflex.
- *Papilloedema*: classical sign, but frequently not present; see Fig. 9.1.

Failing vision and decreasing consciousness are ominous signs.

Causes and pathophysiology

SOL; cerebral oedema; hydrocephalus (➲ Hydrocephalus, p. 425). Cerebral oedema may complicate tumours, infection (cerebral malaria, encephalitis), trauma, or hypoxic cell death. Mechanisms such as ↓ CSF volume initially compensate for slow ↑ in ICP (e.g. slow-growing tumour). However, if ICP continues to ↑ or increase is acute and compensatory mechanisms overwhelmed, brain often becomes laterally displaced and pushed towards foramen magnum at skull base. Medial temporal lobe (uncus) may be forced down through the tentorial hiatus, or a cerebellar tonsil forced through the foramen magnum, causing the brainstem to become compressed (coning). See Fig. 9.2 for anatomy. This → the following progressive changes:

- Level of consciousness decreases, drowsiness → coma.
- Pupils dilate and become unresponsive, first ipsilaterally then bilaterally.
- Posture becomes decorticate, then decerebrate.
- Slow deep breaths → Cheyne–Stokes breathing → apnoea.

Beware of false localizing signs due to ↑ ICP in the absence of focal intracranial pathology: unilateral or bilateral VIth cranial nerve palsy most common; also IIIrd and IVth cranial nerve palsies; uncal herniation may rarely cause an ipsilateral hemiparesis and/or contralateral homonymous hemianopia.

Management

- Sit patient up at 30° to ↑ venous drainage from the brain.
- Ensure adequate oxygenation and optimal ventilation. Aim to keep $PaCO_2$ 4–4.5kPa. Ventilate if necessary.
- Give 20% mannitol 5mL/kg IV over 30–60min to ↓ cerebral oedema.
- Steroids may → rapid improvement within 24h in patients deteriorating with a brain tumour or abscess: give dexamethasone 8–16mg by slow IV injection if severe oedema, or 4mg IM qds for less severe oedema. Steroids are not recommended for ↑ ICP due to head injury.
- Control seizures if present.
- Image brain (CT/MRI) to establish cause of ↑ ICP (if GCS ≤8 intubate to protect airway before scanning).
- Institute specific treatment for proven/suspected aetiology:
  - Manage for cerebral malaria if malaria blood film +ve (➲ Severe malaria, p. 43).
  - If SOL suspected, refer to a neurosurgeon. If ↑ ICP progresses rapidly, urgent decompression with burr holes may be life-saving—see ➲ Space-occupying lesions, p. 425.

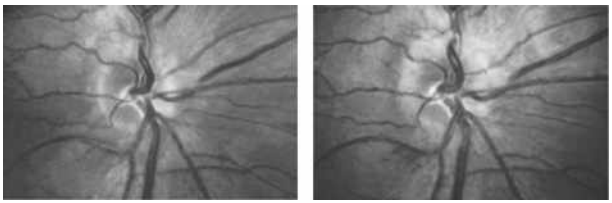


Fig. 9.1 Early stages of papilloedema (left eye). Early nerve fibre layer oedema is first seen superiorly and temporally (left), then inferiorly and nasally (right). Reproduced with permission from Spalton, David, Hitchings, Roger, and Hunter, Paul *Atlas of Clinical Ophthalmology* (3rd edn, Philadelphia, 2005) © Mosby Ltd. 2005.

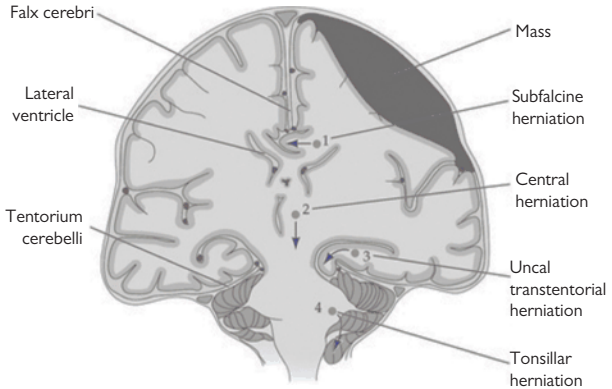


Fig. 9.2 Anatomy of brain herniation syndromes. Reproduced with permission from Blumenfeld, H, *Neuroanatomy through Clinical Cases*, 2002, with permission from Sinauer Assoc. Inc.

Acute bacterial meningitis

Pyogenic (bacterial) meningitis is a medical emergency. It carries a high mortality but early treatment saves lives and reduces neurological sequelae.

Aetiology

Aetiology varies according to age (Table 9.1) and geographically. *Streptococcus pneumoniae* (Gram +ve diplococci) most common cause overall, although pneumococcal conjugate vaccine should ↓ incidence; risk factors include previous head injury, sinusitis, otitis media, and pneumonia. Hib (Gram –ve coccobacilli) meningitis remains common in regions without Hib immunization. *Neisseria meningitidis* (Gram −ve intracellular diplococci) causes most disease in patients aged 2–18yrs in many regions, as well as epidemics (➲ Epidemic meningococcal disease, p. 397). *Streptococcus suis* is an important cause in SE Asia; *Listeria* in pregnant women and the immunosuppressed; *Escherichia coli* and *Klebsiella* spp. in elderly patients and diabetics; *Staphylococcus aureus* following head trauma.

Clinical features

Headache, fever, N&V, lethargy, impaired consciousness, delirium, meningism (stiff neck, photophobia, Kernig's sign; Box 9.4). Acute complications include ↑ ICP, seizures, sepsis, SIADH, subdural empyema, and cerebral abscess (may cause focal neurological signs; lower cranial nerve palsies and urinary retention more common in TBM).

Check the conjunctivae and skin carefully Especially back, buttocks, and soles of feet for any petechiae/rash/purpura; cold extremities and leg pain may also be early signs of meningococcal septicaemia. If present or unsure treat for meningococcal sepsis immediately—may be rapidly fatal.

Diagnosis

Blood culture, FBC, U&E, (+/− malaria test to exclude cerebral malaria). Do LP unless contraindicated (➲ Lumbar puncture and CSF interpretation, p. 113). Send CSF for cell count, Gram stain, culture, protein and glucose estimation, if available; plus AFB microscopy, TB culture, and India ink stain or CrAg (+/− serum CrAg) if differential diagnosis includes TBM or cryptococcal meningitis (e.g. immunocompromised, subacute/chronic history). Guidance for interpretation of CSF indices is shown in Table 9.2.

Table 9.1 Common causes of bacterial meningitis

Age	Most common organisms
<1mth	Group B streptococci, *E. coli*, *Salmonella* spp., *Klebsiella* spp., *L. monocytogenes*
1–3mths	*E. coli*, group B streptococci, *S. pneumoniae*, *H. influenzae*, *N. meningitides*, *L. monocytogenes*
3mths–18yrs	*N. meningitides*, *S. pneumoniae*, *H. influenzae*
18–50yrs	*S. pneumoniae*, *N. meningitidis*, (*S. suis*—especially SE Asia)
>50yrs	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, Gram negative bacilli, (*S. suis*—especially SE Asia)

Box 9.4 Neck stiffness

Involuntary neck stiffness ('nuchal rigidity') is a sign of meningeal irritation/inflammation ('meningism'). In severe cases there may be arching backward of the spine ('opisthotonus'). Patients with meningitis or SAH characteristically lie still not willingly moving their heads, and often complain of a sore head, rather than a sore neck. Clinical signs of meningism may, however, be absent, particularly in infants. Other causes of meningism include streptococcal sore throats, pneumonia, and pyelonephritis.

To test for neck stiffness

- Lie patient flat in bed (remove the pillows) and inform them of what you are doing and reassure them.
- Ask the patient to nod their head so their chin is on their sternum. If a child, you can also ask them to 'kiss their knees'. If the patient can do this, it is unlikely you will find a stiff neck in the next step.
- Facing patient, hold the head securely by putting your hands over the mastoids (behind the ears). Slowly rotate the neck all the way from side to side—this will relax the patient, and enable you to compare rotation (which is not stiff in meningitis) to flexion (which is). Slowly rock head forward to assess for stiffness; repeat this a few times until you are sure. In mild meningitis, it is only the final part of flexion which is stiff—'terminal rigidity'. If neck does not flex fully (chin does not touch sternum), flex head still further forwards and watch whether you can lift patient's shoulders away from bed.

Kernig's sign

Detects painful/inflamed nerve roots ('spinal meningitis') and is similar to straight leg raising. It is sensitive in meningitis, but not very specific. Lie the patient supine and passively flex the knee and hip on one side to 90°. Try passively to straighten knee, until patient winces and knee cannot be straightened further. Pain felt in in low back is suggestive of meningitis; pain felt in hamstrings is less specific. Repeat on other side—result should be the same.

Brudzinski's sign

Little used. In presence of meningeal irritation, neck flexion in an infant sometimes causes involuntary flexion of hips and knees.

Prognosis

Mortality 10–80%; varies with age and aetiology—highest at extremes of age and in patients with sepsis. Long-term complications include deafness, paralysis, visual loss, epilepsy, cognitive impairment.

Management

Antibiotics

- Give immediately if diagnosis suspected. See Box 9.5 for doses.
- Ceftriaxone is preferred first-line empiric treatment in children and adults.
- *Alternatives in adults*: if ceftriaxone not available ampicillin plus co-trimoxazole; or chloramphenicol (➲ Box 9.6, p. 398) plus co-trimoxazole.

Lumbar puncture and CSF interpretation

Indications to LP include suspected meningitis, suspected SAH (➔ p. 419) and symptomatic relief in cryptococcal meningitis (➔ p. 399).

Contraindications: avoid LP if prolonged fits, focal CNS signs (e.g. due to SOL), pupillary dilatation, signs of skin or soft tissue infection at LP site, known or suspected bleeding disorder, or signs of focal neurology or ↑ ICP (➔ p. 390). Focal signs or ↑ ICP risk of brain herniation (➔ Fig. 9.1, p. 391). If possible perform CT prior to LP to look for evidence of brain shift if any of these signs is present. If CT not available consider mannitol and review clinical signs. Do not delay antibiotics while awaiting CT if meningitis suspected.

Interpretation: if possible measure opening pressure. If no manometer available, attach an IV giving set, hold the tube vertically allowing it to fill and measure height of CSF column using a ruler or tape measure. Normal range ~10–20 cm CSF; raised in many conditions; may be very high in cryptococcal meningitis). A guide to CSF analysis is given in Table 9.2. Other useful CSF tests include CrAg (cryptococcal meningitis), VDRL/RPR (syphilitic meningitis), cytology (malignancy).

Table 9.2 Typical CSF indices in cerebral infections of different aetiology

	Normal CSF	Pyogenic bacteria	TB	PAM	Virus	Crypto coccus
Appearance	Clear and colourless	Cloudy or purulent	Clear, yellowish, slightly cloudy	Clear or slightly cloudy	Clear	Clear or slightly cloudy
White cells (majority)	<5/mm³	Usually >200/mm³ (neutrophils)	>10/mm³ (mononuclear)	>200/mm³ (neutrophils)	>10/mm³ (mononuclear)	>10/mm³ (mononuclear)
Glucose	2.5–4mmolL (45–72mg%)	Markedly ↓ or absent	Low	Normal or slightly ↓	Normal	Low
Total protein	0.15–0.4g/L	Raised	Raised	Normal or slightly ↓	Raised	Raised
Microscopy	None	Gram: pus	ZN: AFB present	Wet: motile amoebae	None	India ink +ve

- *Alternatives in children*: if ceftriaxone not available ampicillin (or penicillin) plus gentamicin; or chloramphenicol (➲ Box 9.6, p. 397).
- Add ampicillin for *Listeria* if <3mths, >50yrs old or immunosuppressed.
- Add vancomycin if high prevalence of penicillin-resistant pneumococci.
- Benzylpenicillin is first-line drug for meningococcal meningitis.
- For meningitis following neurosurgery use vancomycin plus ceftazidime.

Supportive care

IV fluids, O_2, pain relief. Treat fever with paracetamol +/− tepid sponging.

Adjunctive steroids for bacterial meningitis

Steroids started shortly before or at the same time as the first dose of antibiotics (e.g. dexamethasone 0.15mg/kg IV qds for 2–4d) have been shown in developed countries to be beneficial in children with Hib meningitis and adults with pneumococcal meningitis.

Evidence from trials in developing countries is conflicting, possibly due to higher rates of HIV, malnutrition, and delayed presentation.

Box 9.5 Antibiotic doses for meningitis

- *Ceftriaxone*: 2g IV bd; children <50kg, 50mg/kg (avoid in neonatal jaundice); IM alternative if no IV access.
- *Benzylpenicillin*: 2.4g IV every 4h for 7d; neonates, 75mg/kg tds; children >1mth old, 50mg/kg 4–6hrly (max. 2.4g every 4h).
- *Ampicillin*: 2g IV every 4h for 10d; neonates, 50mg/kg bd (<7d old) or tds (7–21d old), or qds (21–28d old); children >1mth old, 50mg/kg 4–6hrly (max. 2g every 4h).
- *Co-trimoxazole*: only in combination therapy as above-listed. 10–20mg/kg (based on trimethoprim component) IV daily in 2–4 divided doses.
- *Chloramphenicol*: 12.5–25mg/kg qds; child >1mth old, 12.5mg/kg tds; neonate 14–28d old, 12.5mg/kg 2–4 daily; neonate <14d old, 12.5mg/kg bd; avoid in prematurity/LBW (Box 9.6).
- *Gentamicin*: in combination with ampicillin or penicillin for childhood meningitis. 7.5mg/kg IV od (where resources allow dose may be adjusted according to serum levels).
- *Vancomycin*: 1g IV bd; neonates and children 15mg/kg tds (max. 2g daily). If possible, monitor plasma levels; adjust dose accordingly.
- *Ceftazidime*: 2g IV tds; neonates, 50mg/kg od (<7d old), bd (7–21d old), tds (>21d old); children, 50mg/kg tds (max. 6g daily).

Epidemic meningococcal disease

There are at least nine serogroups of *Neisseria meningitidis* (meningococci), of which three (groups A, B, and C) cause meningitis outbreaks. Serogroup A causes large epidemics every 2–10yrs across the 'meningitis belt' of Africa and hyperendemic meningococcal disease between epidemics in the same region (Fig. 9.3). Types A and C have both been responsible for large outbreaks in the rest of the world. Some strains appear to be more virulent than others. Large epidemics occur when such strains encounter populations of non-immune individuals in areas of poverty during particular climatic conditions (e.g. dry season, dust storm). In between epidemics, the bacteria survive in the community in the nasopharynx of carriers.

WHO advice on surveillance and epidemic control is available at: https://www.who.int/publications/i/item/WHO_HSE_PED_CED_14.1.

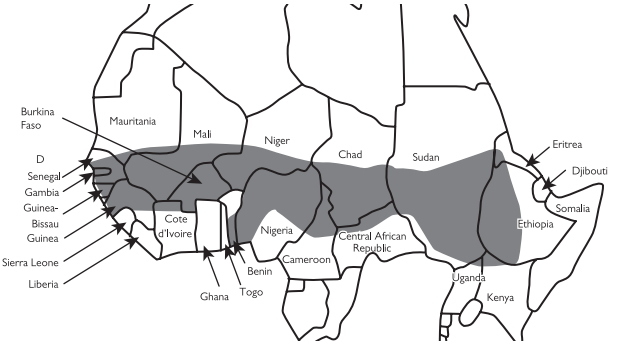


Fig. 9.3 African meningitis belt. Reproduced with permission from World Health Organization, *Control of Epidemic Meningococcal disease: WHO practical guidelines, 2nd edn*, p.6, Figure 2, with permission of WHO.

Treatment

Benzylpenicillin is treatment of choice (➔ Box 9.5, p. 395). Oily chloramphenicol (3g IM stat; children 100mg/kg (max. 3g) stat; repeated after 24–48h if required) is a logistically simple alternative if health resources are stretched in an epidemic (Box 9.6).

Vaccination

This is essential to halt an epidemic once it has begun; kits for vaccination campaigns are available from WHO.

Chemoprophylaxis

This is indicated for household contacts: ciprofloxacin 500mg oral stat; child 2–5yrs 125mg, 5–12yrs 250mg.

Alternative: rifampicin 600mg (children 10mg/kg, infants <1yr 5mg/kg) oral bd for 2d.

Box 9.6 Chloramphenicol

Chloramphenicol has one serious toxicity—aplastic anaemia—with a frequency of ~1 in 10,000 to ~1 in 70,000 courses of therapy (similar to risk of death due to penicillin anaphylaxis: ~1 in 40,000 courses). After due consideration of the risks and benefits, the WHO Expert Committee on Use of Essential Drugs concluded chloramphenicol is essential for modern medical practice in all countries, reaffirming its value in severe bacterial infections such as meningitis.

Viral meningitis

Enteroviruses (e.g. echoviruses and coxsackieviruses) are important causes of epidemic viral meningitis worldwide, while arboviruses (➔ Arboviruses and viral haemorrhagic fever, p. 741) cause sporadic disease in endemic regions. Other causes of sporadic viral meningitis include polio, mumps virus, EBV, HIV, VZV, CMV, and HSV, especially HSV-2. Clinical features are usually less severe than bacterial meningitis. Diagnosis is by CSF examination (➔ Lumbar puncture and CSF interpretation, p. 113), but interpretation may be difficult, particularly if the patient has already received antibiotic treatment. If in doubt, treat with antibiotics to cover bacterial meningitis (➔ Acute bacterial meningitis, p. 392). The causative virus may be apparent during epidemics. In sporadic cases, peripheral signs may suggest the aetiology such as genital or rectal lesions (HSV), skin blisters (VZV), orchitis (mumps, lymphocytic choriomeningitis virus), rashes (enterovirus), parotid swelling (mumps). Treatment is symptomatic. The prognosis is usually good, with complete recovery. HSV may cause recurrent viral meningitis ('Mollaret's meningitis').

Chronic meningitis

TB, cryptococcal, and some other causes of meningitis typically present with a longer history (>7d), headache, and low-grade fever. Confusion and drowsiness are common and may be due to hydrocephalus. Papilloedema, visual symptoms, and nerve lesions (particularly VI, VII, and urinary retention) may occur. Diagnosis is by clinical presentation and CSF examination Although 'chronic', these are still medical emergencies, as delayed therapy → significantly worse prognosis.

Tuberculous meningitis

(➲ pp. 111, 150.) May occur in previously healthy or immunosuppressed individuals. Examine CSF for mycobacteria (AFB microscopy +/− TB culture/Xpert PCR). In HIV the CSF cellular response to TB may be neutrophilic causing confusion with pyogenic meningitis. Look for signs of infection in other sites (e.g. CXR). Treat for TB if suspected. Adjunctive steroids reduce mortality—e.g. dexamethasone IV 0.4mg/kg/d in divided doses reduced over 4wks to 0.1mg/kg/d and then stopped.[1]

Cryptococcal meningitis

Cryptococcal meningitis (➲ p. 112) usually occurs due to infection by *Cryptococcus neoformans* in patients with advanced HIV. More rarely infection with *C. gattii* may occur, including in previously healthy individuals. Diagnosis confirmed by the cryptococcal antigen (CrAg) test on CSF and/or serum (India ink stain on CSF if CrAg not available).

Other causes of fungal meningitis

Other causes of 1° fungal meningitis are rare. Diagnosis is supported by CSF fungal culture +/− serology, specific antigen tests or PCR.

Causes include:

Histoplasmosis

Following 1° infection of the lungs with *Histoplasma capsulatum* (➲ Pulmonary histoplasmosis, p. 202), disseminated infection including meningitis may occur, particularly in the immunosuppressed. Serology and antigen tests may be available. Treatment is with IV amphotericin until afebrile and clinically improving, then itraconazole for a minimum of 1yr.

Coccidioidomycosis

Coccidioides infection follows inhalation of infective spores in arid areas of the Americas including southwestern USA. Clinical features range from a non-specific febrile illness and pneumonia, to disseminated disease and meningitis. Diagnosis is supported by serology. Treatment is with fluconazole 400mg po/IV od (800–1200mg in severe disease. Itraconazole (e.g. 200mg tds) is an alternative.

Eosinophilic meningoencephalitis

Follows CNS infection with the nematodes *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, or *Taenia solium* (➲ Cysticercosis, p. 431). CSF examination shows eosinophilic pleocytosis.

1 Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351:1741–51.

Angiostrongyliasis

Follows ingestion of *Angiostrongylus cantonensis* (rat lung worm) larvae in infected snails or contaminated shrimps, fish, and vegetables that are eaten raw or inadequately cooked (Box 9.7). Widespread in SE Asia and Pacific, but distribution now recognized to be much wider including Asia, Africa, Americas, and Australia. Larvae migrate to the brain → immune response to dead parasites, and then to the eyes and lungs. Presents with acute/intermittent intense headache; malaise; N&V; cranial nerve palsies; +/− meningism. If severe, there may be fever, ↓ GCS, and spinal cord involvement. The eyes are sometimes involved (papilloedema, retinal damage, occasionally larva seen in vitreous). Give sedatives and analgesia. Headache responds to LP every 3–7d. Role of albendazole and steroids remains controversial as disease is normally self-limiting, and dying parasites can elicit a strong immune reaction that can be fatal.

Box 9.7 Prevention of *Angiostrongylus* infection

- Wash all fruit and vegetables (check carefully for slugs/snails).
- Cook food thoroughly (boil prawns/crabs/snails for 3–5min).
- Cover water tanks and containers.
- Pest control including rats, slugs, snails.

Spinocerebral gnathostomiasis

Infection in previously healthy individuals follows consumption of inadequately cooked fish, shrimps, birds, frogs, or reptiles infected by *Gnathostoma spinigerum*. Following infection, larval migration → migratory subcutaneous swellings and eosinophilia. Rarely larvae may migrate to the CNS. This may present with intensely painful radiculitis followed by a rapidly advancing myelitis (paraplegia, urinary retention, or quadriplegia), or as a cerebral haemorrhage. Treatment is as for angiostrongyliasis with albendazole and steroids.

Primary amoebic meningoencephalitis (PAM)

Rare and often fatal infection that follows intranasal infection with *Naegleria fowleri* while swimming in warm fresh water. The amoebae invade the CNS through the cribriform plate → extensive tissue necrosis. Headache occurs first, then fever, meningism, coma, convulsions. The CSF shows neutrophils, red cells, and amoebae on wet microscopy. The prognosis is poor. *Acanthamoeba* cause a similar syndrome, granulomatous amoebic encephalitis, in immunosuppressed individuals.

Management Amphotericin 1–1.5mg/kg IV od. If possible also give amphotericin intrathecally (via a reservoir): start with 0.025mg, then ↑ to 0.25–0.5 mg (*total* intrathecal dose, *not* per kg) on alternate days.

Other causes of chronic meningitis

Other causes include cysticercosis, borreliosis, brucellosis, syphilis, malignancy, sarcoidosis, autoimmune disease (e.g. Behçet's). May also occur 2° to, or concomitant with, other focal CNS infections or encephalitides. It is important to make a definitive microbiological diagnosis whenever possible.

Encephalitis

Encephalitis is inflammation of brain parenchyma. Aetiology is most commonly viral (Table 9.3). Seasonal epidemics occur in many parts of the world causing death and disability in the young and elderly. HSV encephalitis is the most important cause of sporadic viral encephalitis worldwide since it is treatable and therefore should be considered in all cases. However, Japanese encephalitis far outstrips HSV in actual numbers. This and other arboviruses are discussed elsewhere (➲ Arboviruses and viral haemorrhagic fever, p. 741). African trypanosomiasis is an important non-viral cause of encephalomyelitis in endemic areas (➲ African trypanosomiasis, p. 721).

Clinical features

High fever, headache, N&V, followed by convulsions, confusion, and altered conscious level. Meningism (meningoencephalitis), focal neurological signs, abnormal behaviour, and/or ↑ ICP may be present. Severe cases may cause prolonged coma, hemiparesis, dystonia, decorticate/decerebrate posturing, and respiratory failure. Neurological sequelae include mental retardation, hemiparesis, and behavioural problems, and are particularly common after Japanese encephalitis, untreated HSV encephalitis, and postinfectious/vaccination encephalomyelitis.

Diagnosis LP (see ➲ Lumbar puncture and CSF interpretation, p. 113, for contraindications). CSF usually shows lymphocyte predominant pleocytosis, ↑ protein, normal/slightly ↓ glucose. Where available PCR of CSF may confirm specific viral aetiology.

Management Supportive, except for HSV encephalitis (aciclovir (see next paragraph)), CMV encephalitis (ganciclovir or foscarnet), and HIV encephalitis (ART). Control seizures and pyrexia. Beware of respiratory failure and ↑ ICP (➲ Raised intracranial pressure, p. 390). The role of steroids to prevent cerebral oedema is unclear.

Herpes simplex virus encephalitis

Always consider HSV in a patient with encephalitis—it is the only encephalitis for which there is effective treatment. Neurological signs relate to frontal and temporal cortex, and limbic system; they include changes in behaviour, seizures, and focal CNS signs. Where available, MRI shows temporal lobe enhancement. Diagnosis is confirmed by detection of HSV in CSF by PCR. If PCR not available and there is clinical suspicion of HSV infection then treatment should be started immediately. Untreated HSV encephalitis has a mortality of 40–70% and many survivors have neurological sequelae. Aciclovir ↓ mortality and the incidence of sequelae. Delayed treatment greatly ↑ the risk of a poor neurologic outcome.

Equine encephalitis

Three alphaviruses—western, eastern, and Venezuelan equine encephalitis viruses (EEVs)—cause widespread epizootics of encephalitis in horses in the USA, Central America, and northern South America. The EEVs are not common causes of human encephalitis, but Venezuelan EEV has caused large epidemics in both horses and humans in Colombia and Venezuela. Rodents and birds are the 1° hosts; the virus is amplified during horse infections and may subsequently → human encephalitis. Transmission to humans is via *Culex*, *Culiseta*, and *Aedes* mosquitoes. Most infections are subclinical.

There may be a short febrile illness with rigors (in Venezuelan EEV also sore throat, features of URTI, and diarrhoea). Occasionally, illness is biphasic with encephalitis following recovery from febrile phase. Neurological sequelae are unusual in adults, but common in infants and young children with encephalitis, among whom mortality is >10%.

Table 9.3 Important viral causes of encephalitis

Virus family	Examples of viruses causing encephalitis
Adenoviruses	Adenovirus
Alphaviruses	Western, eastern, and Venezuelan encephalitis viruses
Arenaviruses	Lymphocytic choriomeningitis, Lassa, Machupo viruses
Bunyaviruses	Rift Valley fever virus
Enteroviruses	Poliovirus, coxsackieviruses, and echoviruses
Filoviruses	Marburg, Ebola viruses
Flaviviruses	Japanese encephalitis, West Nile, dengue
Herpesviruses	HSV, VZV, EBV, CMV, HHV-6, HHV-7
Orthomyxoviruses	Influenza
Paramyxoviruses	Measles, mumps, Nipah virus, Hendra virus
Retroviruses	HIV
Rhabdoviruses	Rabies, Lyssavirus
Togaviruses	Rubella

Nipah virus encephalitis

Following the first recognized outbreak in Malaysia and Singapore in 1999, Nipah virus now appears to be endemic in South Asia with regular epidemics in India and Bangladesh. Nipah virus is a paramyxovirus closely related to the rarer Hendra virus described in Australia, that exists as a zoonosis infecting pigs and fruit bats. Treatment is supportive; the role of ribavirin remains controversial.

Postinfectious post-vaccination encephalomyelitis

On rare occasions, infection or vaccination may elicit an antiviral immune response → CNS immunopathology and an encephalitic picture. When this occurs it usually follows infection with measles, rubella, herpes zoster, mumps, or influenza and after vaccination with the Semple form of the rabies vaccine (prior to availability of newer tissue/cell culture rabies vaccines; this small risk was usually outweighed by the benefits of vaccination).

Rabies

Human rabies encephalomyelitis is a fatal zoonosis caused by rabies virus species 1 (classic dog rabies and all bat rabies in the Americas) and four species of rabies-related bat lyssaviruses. Most of the world is enzootic for rabies and continuing recognition of bat lyssaviruses in new areas makes the concept of 'rabies-free' countries misleading. Rabies causes 60,000 human deaths each year (18,000–20,000 in India alone). Prolonged anxiety in those exposed to rabies results in considerable morbidity.

Transmission

Transmission to humans is by mammal bites and saliva-contaminated scratches with viral entry though mucosae and broken skin. Domestic dogs are the major reservoir and vector of human rabies throughout most of Africa, Asia, and parts of Latin America. Wild vectors/reservoirs include cats, wolves, foxes, jackals, skunks, mongooses, raccoons, vampire bats (Caribbean and Latin America only), and fruit- and insect-eating bats. Bat bites anywhere are a potential risk of rabies infection. Rodents pose negligible, if any, risk. Human-to-human transmission occurs through infected transplants of corneal and solid organs from unsuspected rabies-infected donors. Infected mothers may deliver healthy babies. Inhalation was documented in a single laboratory accident.

Clinical features

The virus spreads from the wound along nerve axons to reach the CNS causing fatal encephalomyelitis. The incubation period is usually a few months, but varies from 4d to many years. The first symptom is often itching in the dermatome of the healed bite. Within a few days, symptoms of either furious or paralytic rabies develop.

Furious rabies

Commonest presentation. Symptoms include headaches, fever, confusion, and fluctuating periods of excitation with hallucinations. Hydrophobia is pathognomonic: attempts to drink water (and/or drafts of air, aerophobia) → jerky spasms of inspiratory muscles associated with indescribable terror. Spasms may → convulsions → cardiorespiratory arrest. Other features incl. cranial nerve defects, and signs of autonomic/hypothalamic hyperactivity, such as hypersalivation, lacrimation, fluctuating BP and temperature. Complications during intensive care incl. pneumonitis, myocarditis, cardiac arrhythmias, pneumothorax, haematemesis, ↑ICP, diabetes insipidus, and rarely SIADH.

Paralytic or dumb rabies

Presents as ascending flaccid paralysis, accompanied by pain, fasciculations, and mild sensory disturbances → paraplegia, sphincter involvement, and fatal paralysis of bulbar and respiratory muscles.

Diagnosis

Suggested by neurological symptoms following a mammal bite in an endemic area. Laboratory confirmation in a patient during life is by PCR (saliva, skin biopsy), virus isolation (saliva, brain, CSF), and immunofluorescence of viral antigen (skin punch biopsies). Neutralizing antibody response is often absent or delayed.

Prognosis and treatment

Furious rabies encephalomyelitis is almost invariably fatal within a few days and paralytic rabies within 30d. There are a few documented survivors from rabies encephalomyelitis, almost all with devastating sequelae. Recovery with return to independent life is reported in only three people, 2 of whom had had previous vaccination. Experience suggests that intubation and intensive care is appropriate only for patients with early symptoms of encephalomyelitis after infection with American bat rabies virus, esp. if rabies neutralizing antibody is detectable. Otherwise offer active palliative treatment with sufficient analgesia and sedation to relieve pain and terror. No antiviral or other specific treatment has proved successful. The much-publicized 'Milwaukee protocol' is not effective.

Prevention

Vaccination of domestic dogs, and, in some countries, wild foxes, jackals, raccoons, skunks, etc., is key to control. In humans, pre- (PrEP) and post-exposure prophylaxis (PEP) have proved highly effective.

Rabies post-exposure prophylaxis (PEP)

PEP consists of immediate wound cleaning; tissue/cell culture vaccine; and if not previously vaccinated, rabies immunoglobulin (RIG). It is extremely effective in preventing rabies encephalomyelitis. Economical multi-site intradermal (ID) regimens have proved safe and effective and have made the expensive vaccines more affordable.

Indications for PEP

Decision to start PEP depends on the nature of exposure (Box 9.8). Intact skin is a barrier to infection. If in doubt give PEP since rabies is fatal.

Immediate management

- *Clean the wound*: this kills virus in superficial wounds. Scrub wound with soap/detergent and wash under running water for >5min. Irrigate with virucidal agent—povidone iodine (or 40–70% alcohol). Debride as necessary, but delay suturing if possible.
- Give anti-tetanus toxoid.
- Consider prophylactic antibiotics.
- *Give vaccine*: see Boxes 9.8, 9.9 and 9.10 and Fig. 9.4.
- *Give RIG if indicated* (Box 9.8)—human RIG 20IU/kg or equine RIG 40IU/kg. Infiltrate whole dose or as much as possible into and around the wounds; dilute if necessary to ensure multiple or very large wounds are infiltrated. Avoid injecting large volumes of RIG into areas with limited tissue (e.g. fingers) to prevent compartment syndrome. Inject residual RIG IM distant from a vaccination site, not into the buttock. Anaphylaxis is extremely rare. If supply of RIG is limited consider injecting wounds only, *except for* those with severe exposure: with multiple bites, deep wounds, or bites to highly innervated parts of the body, such as the head, neck, and hands; patients with severe immunodeficiency; if the biting animal has confirmed or probable rabies; or where bites, scratches or exposure of a mucous membrane are caused by a bat.

Box 9.8 Indications for post-exposure vaccine and rabies immunoglobulin

Minor exposure

Nibbling (tooth contact) with uncovered skin, or minor scratches or abrasions without bleeding:

- Start vaccine immediately.
- Stop treatment if the dog or cat can be observed and remains healthy 10d following exposure; or if animal's brain is –ve for rabies by appropriate tests.

Major exposure

Single or multiple bites/scratches that break the skin; licks on broken skin; licks/saliva on mucosae, or physical contact with bats. Greatest risk is from bites on head, neck, hands, or multiple bites.

- Immediate RIG and vaccine.
- Stop treatment if the dog or cat can be observed and remains healthy 10d following exposure; or if animal's brain is –ve for rabies by appropriate tests.

Box 9.9 Rabies tissue culture vaccines

Note: vaccine dose (mL) per injection depends on the vaccine:

- *Verorab® (Sanofi-Pasteur)*: reconstitute in 0.5mL (ID dose 0.1mL/site).
- *Rabipur®/Rabavert® (GSK)*: reconstitute in 1mL (ID dose 0.2mL/site unless stated).

There is no international consensus on the 'best' vaccine regimens.

The highly immunogenic regimens given here are selected from the 13 suggested by WHO. Choice of regimen depends on the importance of time, cost, and ability to give ID injection without wastage. National guidelines vary accordingly.

Pre-exposure rabies vaccination

Vaccination is strongly recommended for inhabitants of and travellers to rabies enzootic countries or and those with occupational risk. Confers long-lasting recall of antibody levels in response to boosting after subsequent exposure. There are no reported failures of combined pre-exposure and post-exposure boosting. For Pre-exposure vaccine regimens see Box 9.11.

Box 9.10 Selected PEP rabies vaccine regimens

Regimens for patients who have NOT previously completed a course of rabies vaccine:

1. Four-dose IM method

Give whole vial IM (deltoid) on days 0, 3, 7 and 21
(Five doses if immunosuppressed: Give whole vial IM (deltoid) on days 0, 3, 7, 14 and 30)

2. Three visit ID method (more immunogenic, recommended by WHO but not in UK)

- Day 0: divide whole vial* between four ID sites (deltoids and suprascapular or thighs; see Fig. 9.4)
- Day 7: divide half vial ID (0.1 or 0.2mL*) between two sites.
- Day 28: give ID dose (0.1 or 0.2mL*) at 1 site.

Rabies post-exposure vaccine booster in those who have had ≥ 3 doses of rabies vaccine previously (RIG not needed)

1. IM method

Give whole vial IM on days 0 and 3.

2. Single day ID method (recommended by WHO but not in UK)

Divide whole vial* between four ID sites (deltoids and suprascapular or thighs) (0.1 or 0.2mL per site*) on day 0.

* See Box 9.9 for ID doses (mL) for each vaccine.

Box 9.11 Selected pre-exposure rabies vaccine regimens

- *Three visit* IM dose on days 0, 7 and 21-28
- (The same regimen can be given economically ID if aseptic vial sharing is possible).

Emergency short course for those about to travel:

- Three visit IM (*recommended in UK*): One dose on days 0, 3 and 7 and additional dose anytime after one year if risk will continue.
- Single day ID regimen *(immunogenic but not officially recommended):* Divide whole vial between four ID sites (deltoids and suprascapular or thighs) (0.1 or 0.2mL per site*) on day 0, and an additional IM dose or 0.2mL ID on return from travel at any time after 2 weeks if risk continues.

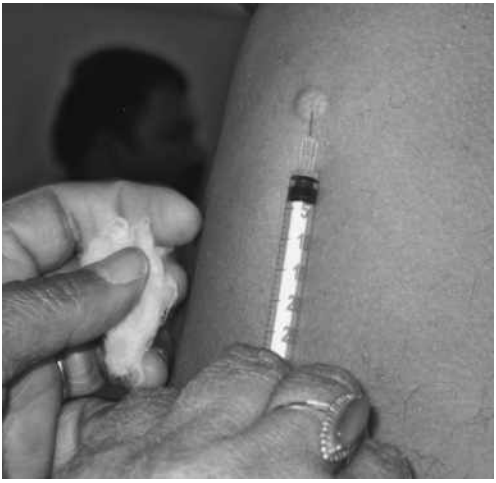


Fig. 9.4 ID administration of rabies vaccine. Use 1mL syringe intradermally to raise an immediate bleb in the skin. Method is as for BCG vaccination or Mantoux test. If injected too deep (no bleb), withdraw needle and repeat at adjacent site. ID administration sites: deltoids, suprascapular, thighs.

References

WHO 2018. World Health Organization Expert Consultation on Rabies. Third Report. Technical Report Series 1012 http://apps.who.int/iris/bitstream/handle/10665/272364/9789241210218-eng.pdf?ua=1

PHE 2018 Rabies: the green book, chapter 27. Gov UK https://www.gov.uk/government/publications/rabies-the-green-book-chapter-27

Tetanus

Contamination of a wound with the bacterium *Clostridium tetani* can → severe neurological sequelae due to toxin production. The toxin tracks up nerves innervating local muscles, entering the CNS; it also enters the blood and passes to other muscles where it is again transported via peripheral nerves to the CNS. There it blocks release of inhibitory neurotransmitters → widespread activation of both motor and autonomic nervous systems. Muscles of the jaw, face, and head are involved first because of the shorter axonal paths, but all muscle groups become involved in most cases. Activation of opposing groups → rigidity. Protracted uncontrolled muscular spasms of the chest → ineffective breathing and hypoxia. Death is due to respiratory complications, circulatory failure, or cardiac arrest. In patients with access to ICU support, autonomic instability and arrhythmias become the most common causes of death.

Tetanus is easily prevented by vaccination

Its incidence worldwide is directly related to immunization coverage. Where immunization coverage is high it is rare, but in regions where coverage is low it is a common condition, particularly of neonates who become infected at birth. 80% of cases occur in Asia and sub-Saharan Africa. Immunization of pregnant women prevents neonatal tetanus.

Transmission

C. tetani spores are ubiquitous in the environment and can infect even the most trivial cuts, typically on feet, legs, and hands. Neonatal infection occurs via the cut umbilicus from the use of a dirty knife or the practice of applying dung to the stump. Otitis media is a common infection portal in older infants.

Incubation period and period of onset

Incubation period is usually 7–10d, but varies; many patients cannot recall the injury. *Period of onset* (between first symptom and onset of spasms) varies between 1 and 7d and is a good prognostic indicator—the shorter the interval, the more severe the disease.

Clinical features

Diagnosis is clinical. The first symptom is often trismus (masseter rigidity → difficulty opening mouth) (Box 9.11). Other muscle groups then become rigid, including muscles of face (→ characteristic look: *risus sardonicus*), skeleton (→ difficulty in breathing; opisthotonos; rigid limbs), and swallowing (→ dysphagia + aspiration). Spasms of ↑ rigidity occur in more severe disease, either as reflex response to stimuli (touch, sounds, sights, emotions) or spontaneously; may be localized (e.g. to a limb or head and neck) but are more usually generalized (involving all muscle groups); and brief and mild or prolonged and very painful. Prolonged thoracic spasms may → respiratory failure; laryngeal spasms → death from anoxia (Box 9.12). In severe disease, fever, tachycardia, and cardiovascular instability are common, mainly due to involvement of the autonomic nervous system—see Box 9.12.

Neonatal tetanus

See ➲ Neonatal tetanus, p. 31.

Box 9.12 Grading of tetanus severity (modified Ablett score)

- *Grade I (mild)*: mild to moderate trismus; general spasticity; no respiratory problems; no spasms; little or no dysphagia.
- *Grade II (moderate)*: moderate trismus; well-marked rigidity; mild to moderate, but short-lasting spasms; moderate respiratory failure with tachypnoea >30–35/min; mild dysphagia.
- *Grade III (severe)*: severe trismus; generalized spasticity; reflex and often spontaneous prolonged spasms; respiratory failure with tachypnoea >40/min; apnoeic spells; severe dysphagia; tachycardia >120/min.
- *Grade IV (very severe)*: features of grade III plus violent autonomic disturbances involving the cardiovascular system. These include: episodes of severe ↑ BP and tachycardia alternating with relative ↓ BP and bradycardia; severe persistent ↑ BP (diastolic >110 mmHg); severe persistent ↓ BP (systolic <90mmHg).

Data from Thwaites CL, Yen LM, Glover C, et al. Predicting the clinical outcome of tetanus: the tetanus severity score. *Trop Med Int Hlth*, 11(3), pp. 279–87, https://doi.org/10.1111/j.1365-3156.2006.01562.x, 2006.

Box 9.13 Complications of tetanus

- *Respiratory*: collapse; aspiration, pneumonia (including due to Gram – ve organisms); anoxia due to prolonged laryngeal spasm; severe hypoxia and respiratory failure in severe tetanus if patient is not paralysed and ventilated; unexplained tachypnoea and respiratory distress; ARDS. Complications also include those of tracheostomy and prolonged ventilation.
- *Cardiovascular—mostly mediated by autonomic nervous system*: persistent tachycardia, ↓ BP or ↑ BP; labile BP; severe peripheral vasoconstriction → shock-like state.
- Autonomic storms characterized by sudden sinus tachycardia + severe ↑ BP → sudden bradycardia and ↓ BP. They may precede cardiac arrest. ↑ vagal tone is shown by sudden bradycardia—tracheal suction may lead to an arrest. Dysrhythmias include SVT, junctional rhythms, atrial and ventricular ectopics, short bursts of self-resolving VT. Hyperthermia may occur (hypothermia is rare).
- *Sudden death*: caused by many of the above-listed complications, massive PE, or unidentified event.
- *Sepsis*: most commonly nosocomial.
- *Renal insufficiency.*
- *Mid-thoracic vertebral fracture*: occurs during severe spasms; there are usually few sequelae (the muscle stiffness prevents painful movements) and healing occurs without incident.

Prevention

By active vaccination of children and pregnant women (➲ Tetanus immunization, p. 842); good wound toilet and passive vaccination following injuries; provision of clean facilities for childbirth.

Management of tetanus

Management of severe tetanus can be extremely difficult and it carries a high mortality. Ideally manage *all* patients in an ICU setting. If an ICU is not available, careful attention to supportive care including ventilatory support can markedly improve the prognosis. The overall aims of care are prevention of toxin uptake; control of spasms; and supportive care to prevent hypoxia, maintain fluid, electrolyte, and acid–base balance, and provide circulatory support in grade IV disease.

Central venous access is useful if available. If ventilators are limited, they should be reserved for patients with grade IV disease, grade III disease uncontrolled by sedatives, or serious respiratory complications.

On admission all patients should receive

- *Antiserum (antitoxin)*: there is no international consensus on the optimum regimen. If available, give human tetanus immunoglobulin 5000–10,000U IM, depending on the preparation (some authorities recommend a dose as low as 500U). Alternatives include equine antiserum 10,000U IM (*be prepared for anaphylactic reaction* to equine antiserum and have treatment ready); or human intravenous immunoglobulin (IVIg; dose 400mL 5% IVIg (or 200mL 10% IVIg) if <50kg; 800mL 5% IVIg (400mL 10% IVIg) if ≥50kg).
- *Antibiotics*: metronidazole 500mg oral or IV tds for 7–10d (poorer alternative: benzylpenicillin 1.2g IM or IV tds for 8d).
- *Local infiltration of antiserum*: of uncertain efficacy, but recommended in some parts of the world.
- *Magnesium*: can help reduce need for muscle relaxants and sedatives and may be helpful in reducing autonomic dysfunction. Give loading dose of $MgSO_4$ 40mg/kg IV over 30min; followed by IV infusion of 2–3g/h for patients >45kg and 1.5g/h for patients ≤45kg until control of spasms achieved.
- *Wound debridement*: performed after other steps, to remove necrotic tissue. Delay suturing.
- *Tetanus vaccination*: before discharge, as an attack of tetanus does not immunize the patient.
- Prevent, detect, and promptly treat any infection.

Critical care and nursing is essential

- *Detect early hyperpyrexia*: treat with paracetamol and wet cloths.
- ↓ *external stimuli*: physical examination must be gentle.
- *Keep airway patent*: use *gentle* suction to remove saliva and secretions at the back of the throat.
- *Take exquisite care of tracheostomy*: gently and frequently change patient's posture.
  - *Use physiotherapy to keep lungs patent*—give small IV bolus of diazepam before physiotherapy.
  - In paralysed patient, perform physiotherapy when the action of pancuronium (or gallamine) is at its maximum.
- Optimize nutrition: 3500–4000cal/d (incl. >100g protein) by NGT.

Subsequent management

Depends on the severity of the condition.

Grade I

- Beware of complications of a septic wound.
- Observe carefully—grade I can → more severe disease.
- For sedation/muscle relaxation give diazepam, e.g. 5mg oral/IV tds (children 0.1–0.3mg/kg every 1–4h). Alternative: chlorpromazine 50–150mg (adult), 25mg (child), or 12.5mg (neonate) IM qds (phenobarbital can be added if essential).

Grade II

Treat as for grade I, but ↑ sedation/muscle relaxation:

- ↑ diazepam dose up to fourfold in adults (do not exceed 80–100mg/d because of respiratory depression). Give by slow IV infusion over 24h. The ideal sedative/muscle-relaxant schedule ensures continuous sedation such that patient can sleep, but can be woken up to obey commands. Objective guide is relaxation of abdominal muscles.
- Perform a tracheostomy (may prevent death due to prolonged laryngeal spasm and anoxia).
- If laryngeal spasm occurs, promptly give chlorpromazine 50mg IV (alternative: diazepam 10–20mg IV).

Grade III

Treat as for grade II, but also paralyse and ventilate:

- ↓ diazepam dose (e.g. to 30–40mg over 24h for adults). Give pancuronium 2–4mg (poorer alternative: gallamine 20–40mg) IV, titrated for each patient to give sufficient neuromuscular blockade for efficient ventilation. Initially, give every 1–1.5h (1st 1–2wks), then extend interval as the patient improves. Check with periodic arterial blood analysis, if available.
- Spasms still occur under paralysis, but they need not affect ventilation; pancuronium can be stopped when spasms cease.
- Continue ventilation until patient can be weaned off.

Grade IV

Treat as for grade III, with addition of drugs that act on the cardiovascular system (CVS) if deemed *essential* for grossly deranged haemodynamics:

- If ↓ BP—give IV fluids; if ineffective or contraindicated, use dopamine to keep systolic BP >100mmHg.
- If ↑ BP (systolic >200, diastolic >100mmHg) give propranolol 5–10mg po or nifedipine 5mg sublingual.
- Treat bradyarrhythmia or persistent tachyarrhythmias.

Stroke

A rapidly developing focal loss of cerebral function that lasts >24h, with no history of recent head injury. In industrialized world usually caused by thrombosis/embolism leading to cerebral infarction (>80%). The situation differs in the developing world (Box 9.14). ~20% of stroke patients die within the 1st month; mortality is higher after haemorrhagic stroke than following thrombosis.

Transient ischaemic attack (TIA) Acute loss of focal cerebral or monocular function lasting <24h. Associated with ↑ risk of stroke (>5%/yr) and death, 2° thromboembolic events (stroke or MI, >10%/yr).

Risk factors for stroke Include hypertension, IHD, atrial fibrillation, TIAs, peripheral vascular disease, DM, smoking.

Clinical features

History of sudden event is crucial in establishing diagnosis. Neurological deficits vary according to the anatomy of stroke (Table 9.4 and Fig. 9.5). Possible to relate clinical features to known anatomy of particular cerebral blood vessels, but collateral blood supply may make this difficult. Infarcts affecting cerebral hemisphere may cause contralateral hemiparesis (→ upper motor neurone paralysis after initial spinal shock), sensory loss, homonymous hemianopia, and/or dysphasia. Infarcts affecting subcortical structures, e.g. thalamus and basal ganglia, can cause mixed or isolated motor and/or sensory defects or ataxia. Brainstem infarcts can have profound effects: quadriplegia, visual and/or respiratory problems, locked-in syndrome. There is often a transient hypertension that settles.

Management

- Ensure adequate airway, oxygenation, and circulation.
- If ↓ BP, consider bolus normal saline 250–500mL.
- Determine exact time of onset—critical to establish eligibility for acute thrombolysis if available (Box 9.13).

Do a non-contrast head CT scan to rule out haemorrhage. *If CT shows no blood* consider thrombolysis (Box 9.15). If thrombolysis not indicated or available give aspirin 150mg daily.

Box 9.14 Main causes of stroke in sub-Saharan Africa

- Hypertension (haemorrhagic stroke).
- Atherosclerosis (thrombotic stroke).
- Rheumatic heart disease (embolic from left atrium),
- *Others*:
  - Haemoglobinopathies (including sickle cell disease).
  - HIV.
  - SAH.
  - Unexplained (mainly young persons).

Table 9.4 Overview of stroke anatomy

Vascular territory affected by stroke	Clinical manifestations
Middle cerebral artery (MCA)	Contralateral hemiplegia, hemianaesthesia, homonymous hemianopia, gaze preference to ipsilateral side. Global aphasia (when dominant hemisphere involved). Constructional apraxia, general or unilateral neglect, dysarthria
Anterior cerebral artery (ACA)	Paralysis of opposite foot and leg, paresis of opposite arm, cortical sensory loss over toes, foot and leg, urinary incontinence, contralateral grasp reflex, hypertonia
Anterior choroidal artery (AChA)	Contralateral hemiplegia, hemianaesthesia, homonymous hemianopia
Proximal posterior cerebral artery (PCA)	IIIrd nerve palsy with contralateral ataxia or contralateral hemiplegia
Distal PCA	Contralateral homonymous hemianopia with macular sparing, disturbance in memory
Vertebral-basilar artery	Unilateral or bilateral motor/sensory deficits, accompanied by cranial nerve and brainstem signs

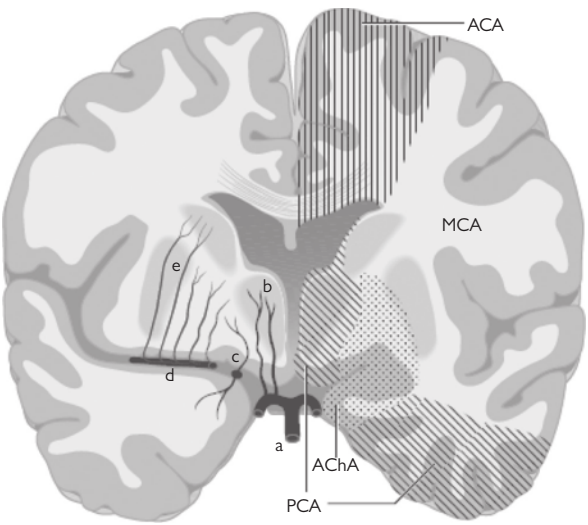


Fig. 9.5 Coronal view of the cerebral hemispheres. ACA, anterior cerebral artery; AChA, anterior choroidal artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; a, basilar artery; b, thalamoperforator, which originate in the PCA; c, AChA; d, MCA; e, lenticulostriate arteries.

- Slowly and carefully lower BP by no more than 10–20% if very high (>120mmHg diastolic; >220mmHg systolic).
- Take great care of the airway in the unconscious patient.
- Turn the patient every 4h to avoid bedsores.
- Ensure adequate nutrition and hydration.
- Look for and treat any treatable cause (e.g. cardiac source of emboli, giant cell arteritis).
- Watch out for causes of neurological deterioration—see Box 9.16.
- If evidence of cerebral oedema, consider mannitol.
- *Think about rehabilitation* early in the patient's illness (➲ Stroke rehabilitation, p. 414). Do not ignore this issue until the patient has developed joint contractures that will prevent physical recovery.

Stroke prevention

Recovery for most patients is rarely complete and 1° prevention is important. ↓ risk of strokes by controlling risk factors, particularly hypertension and smoking. In patients who have had TIAs or previous strokes, it is particularly important to control BP and ↓ risk of further thrombotic events by giving aspirin 75mg oral od. Assuming no contraindications, and the availability of safe, reliable monitoring of INR (often not available in low-resource settings), anticoagulation is recommended for patients with AF, procoagulant clotting disorders, or recurrent DVT. Directly acting oral anticoagulants (e.g. apixaban, rivaroxaban, dabigatran) may be an available alternative in some settings, and don't require monitoring.

Stroke rehabilitation

Without rehabilitation and physiotherapy, the patient risks spending the rest of their days in a wheelchair or bedbound. It is essential to start physiotherapy as soon as the patient is medically stable, to give the best chance of regaining hand and arm function and of walking. Aim to regain independence.

Rehabilitation is a 24h process. Good work during the day can be ruined by a night in a bad position. Teach patient's relatives the basics of physiotherapy so that they can look out for bad positioning and help patient perform exercises. Initially, encourage patient to participate in therapy for ~20min, 3×/d. This can ↑ with time. Physiotherapy should never be painful. 'No pain, no gain' has no place in rehabilitation.

General guidelines for stroke rehabilitation

- The stroke patient initially has ↓ tone. At onset, rehabilitation attempts to ↑ power in limbs. However, over time, tone may ↑ → spastic limbs with fixed deformities. A hand bunched up and curled under the arm is useless. Gentle repetitive exercises should be able to ↓ tone. Work on opposite movements to those that cause the hand to bunch up—extension at shoulder, elbow, wrist, and fingers.
- Normal movement is easier if the person is completely relaxed. This is accomplished by supporting the whole body (Fig. 9.6).
- Aim of stroke rehabilitation is normal movement. Some patients will neglect one side—ensure that patient is able to see both arms and hands at all times. Reinforce message that they are symmetrical. The patient can practise actions with weak limbs (e.g. picking up a cup, stepping from one foot to the other while sitting) by carefully noting action with normal limb, and then copying this with weak limb.

Box 9.15 Thrombolysis for acute non-haemorrhagic stroke

Thrombolysis with recombinant tissue plasminogen activator is licensed for treatment of acute ischaemic stroke within the first 4.5h after stroke onset. It has been shown to ↓ mortality and ↓ morbidity despite a small ↑ risk of intracranial haemorrhage. It should only be considered in centres with appropriate clinical and neuroimaging expertise, therefore not appropriate in most low-resource settings. Contraindications include delayed presentation, recent surgery, head trauma, GI or urinary haemorrhage, seizure at stroke onset, bleeding disorder, severe uncontrolled hypertension.

Box 9.16 Causes of neurological deterioration after stroke

- *Local*: extension of thrombus; recurrent embolism or haemorrhage; haemorrhagic transformation of the infarct; post-haemorrhage vasoconstriction; further ischaemia; cerebral oedema; brain shift and herniation; hydrocephalus; epileptic seizures.
- *General*: hypoxia (pneumonia, PE, cardiac failure); hypotension; infection; dehydration; hyponatraemia; hypoglycaemia or hyperglycaemia; drugs; depression.

- Repetition of a movement over a period reinforces plastic adaptation. After a stroke, the brain has to relearn how to do things. It needs to practise. However, repetition can strengthen both bad and good habits, so it is essential to get the practised movements right.

Early stage

- Support and position the patient carefully, paying particular attention to the hemiplegic shoulder to ↓ risk of injury. Fig. 9.6, nos. 1–3, show how to cushion the patient.
- Relatives or nurses should roll patient carefully (no. 4). As patient becomes stronger, teach rolling from side to side, and then to get up from lying (nos. 5 and 6). Patient will often need help.
- Frequent changes in position are good.
- Aim to maintain muscle length (prevent contractures) with *gentle* passive/active movements into extension, taking particular care over Achilles tendon, and flexors of elbow, wrist, and fingers.
- Encourage selective and controlled movements. It is better to work slowly to get good control of arm and hand movements than to be able rapidly to regain function with gross abnormal limb movements.

Basic principles for this early stage

- Aim for symmetry: sit patient in a good position with adequate support. Set arms forward. Sit patient out for short periods if trunk control is poor. Practice transferring weight from side to side → easier for patient to shift weight from one leg to the other while learning to walk again.
- *Aim for good control of movement*: patient needs to be able to control transfer of body weight in sitting/standing. Patient needs to lean forward to get up, using a high seat initially. With progress, seat can be lowered, before trying a chair.
- *Aim for trunk control*: in sitting, before trying to stand and especially during sitting → standing.
- *Aim for balance*: in standing and stepping before walking.

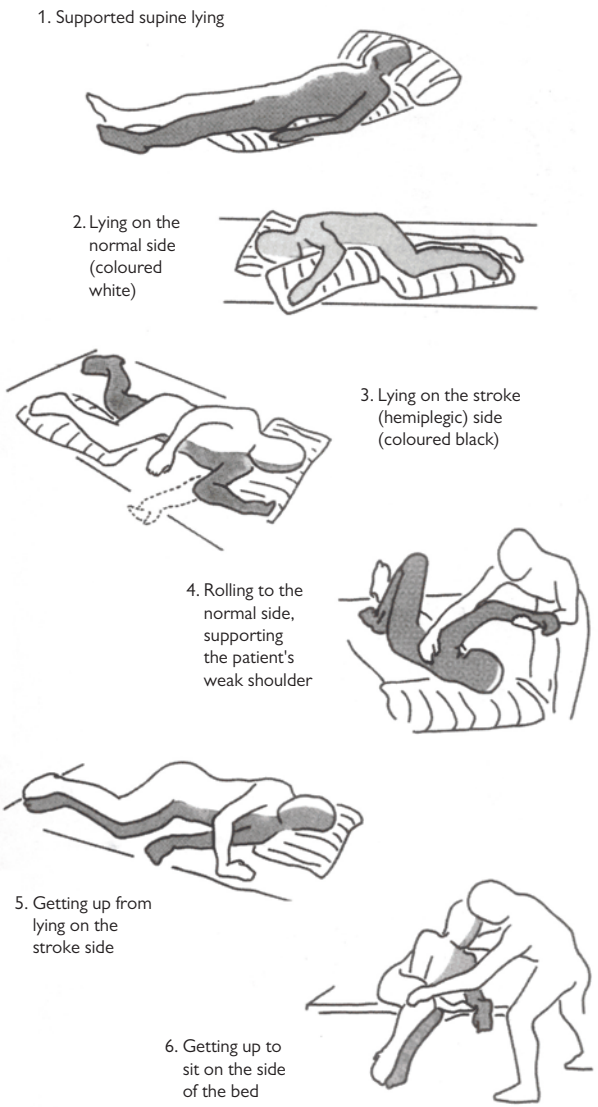
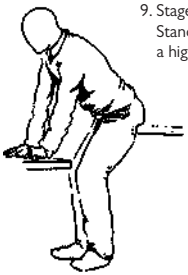


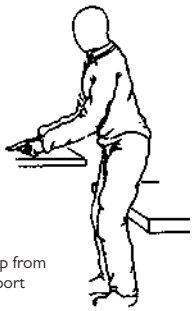
Fig. 9.6 Patient support and positioning in stroke rehabilitation.

7. A good sitting posture, with the arms out in front

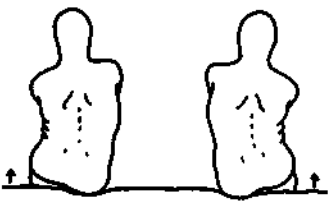
8. Temporary support for a weak shoulder



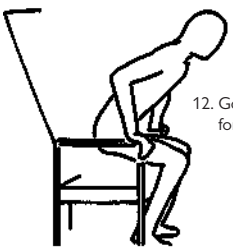
9. Stage 1. Standing up from a high support



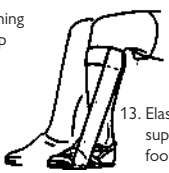
10. Stage 2. Standing up from a low support



11. Improving trunk control – taking the weight on each side



12. Good positioning for standing up



13. Elasticated support for foot drop

Fig. 9.6 *(continued)*

Walking stage

- *Aim for normal gait*: equal stride length and equal time on both sides.
- The patient may require support on one or both sides.
- Start walking with the *unaffected* leg. This means that patient must have already learned to shift weight from leg to leg.
- *Walking aids*: use a wheeled frame/rollator or a normal walking stick (a quadruped stick should be a last resort).
- Patient may require help with a 'drop foot'.
- Use mime, gestures, repeating and rephrasing movements, and physical prompts to help the patient. Allow time for slow synapsing.
- Little and often is a better way to build stamina and sustain carry-over from one session to another.

Box 9.17 Some 'don'ts' for stroke rehabilitation

- *Do not ask the patient to try harder*: *avoid* effort as it ↑ tone and gross patterns of movement.
- *Do not ask the patient to squeeze a ball*: this encourages arm flexors that are already too strong.
- *Avoid a painful shoulder*: do not make any arm movements unless whole shoulder, including the scapula, is relaxed and supple. *Support for a weak arm* may be useful temporarily (e.g. while concentrating on walking).
- *Never lift under stroke arm or pull it*: muscles that hold the shoulder are weak and the joint is easily dislocated.
- *Prevent dislocation*: support forearm and hand forwards with natural weight through the elbow.

Subarachnoid haemorrhage

An acute bleed into the subarachnoid space → a sudden intense headache ('like being hit on the back of the head'), sometimes accompanied by N&V. Most cases of SAH are caused by ruptured aneurysms. Other causes are mycotic aneurysms (due to endocarditis) and arteriovenous malformations; 15% have no identified cause. Some SAHs are preceded by minor herald bleeds that also elicit an intense headache +/– meningism or back pain. If suspected, refer for evaluation since surgical treatment at this time may prevent a later severe bleed. Rebleeding occurs in >30% of cases; it is a common cause of death.

Clinical features

The conscious level may be ↓. The more severe the bleed, the lower the conscious level, and the worse the prognosis. Other features include: headache with meningism; vomiting; seizure. Focal signs are rare. The patient is often irritable and drowsy; the headache may last for weeks. Complications include vascular spasm → cerebral ischaemia.

Beware

↓ conscious level, the appearance or worsening of a neurological deficit (e.g. development of hemiparesis, dilatation of a pupil), or systemic changes such as ↑ BP that may indicate ↑ ICP.

Diagnosis

Diagnosis is by clinical findings with LP (and early CT scan if available). The CSF is uniformly blood stained in the first few days. Xanthochromia (straw-coloured supernatant) may be present from 6h after bleed onset up to 14d. Do not delay LP if differential diagnosis includes meningitis.

Management

Often involves neurosurgery to evacuate an intracerebral haematoma or clip the aneurysm. Medical treatment involves extended bed rest, analgesia, sedation (beware masking of ↓ conscious level), and cautious control of hypertension. Give IV hydration (3L/d). Nimodipine (60mg po every 4h for 2–3wks, starting within 4d of haemorrhage) ↓ the incidence of vascular spasm.

Subdural haemorrhage

A slow venous bleed that follows damage to veins crossing from the cortex to venous sinuses. May even occur after minor trauma in those predisposed: elderly, alcoholics, people with clotting disorders, epileptics. Presentation can occur months after the forgotten accident as chronic bleeding slowly ↑ size of the haematoma (Fig. 9.7).

Clinical features

Common acute symptoms include headache, vomiting, fluctuating levels of consciousness; less commonly, mood changes, irritability, incontinence, drowsiness. Signs may include changes in pupil size, distal limb weakness, and ↑ reflexes; less commonly, seizures and dysphasia.

Management

Requires a neurosurgical opinion and, if possible, a CT scan → evacuation through burr holes in most cases (Box 9.18). Minor haematomas may resolve spontaneously. With appropriate management outcome is good in all ages: >90% return to normal, so it is important to consider the diagnosis in a confused elderly person.

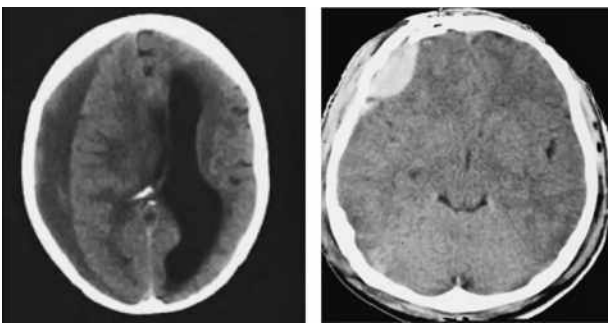


Fig. 9.7 Typical crescent-shaped hypodense chronic subdural haematoma (left); typical lens-shaped acute extradural haematoma (right).

Box 9.18 How to do a burr hole

Incision (Fig. 9.8)

- Shave scalp if there is time.
- Local anaesthetic not usually necessary.
- Make a 4-cm incision over the site of fracture or injury: this is usually in the temporal region (just above the zygomatic arch), where a curved incision is made so that it can be enlarged.
- Incise right down to the bone. Do not stop to control bleeding.

Scrape back the pericranium (periosteum)

Us a periosteal elevator (or similar instrument) to expose skull. Insert a mastoid retractor—this will stop all bleeding (Fig. 9.9). Leave retractor in.

Perforate the bone using a perforator

- Dark blood will ooze out.
- The dura will not be seen as it is stripped away by the blood clot.
- Do no more than *just* perforate the skull (Fig. 9.10).
- This will create a conical hole.

Enlarge the perforation using a burr

- The burr will enlarge the hole so that it is nearly cylindrical.
- *The blood clot will immediately ooze out.*
- Suck blood away by applying a sucker to the burr hole but do not insert sucker into cavity. This will cause more bleeding and might damage the brain. (See Fig. 9.11.)

Aftercare

- It is now safe to transfer the patient to a neurosurgical unit.
- Leave the scalp retractor in; organize for its return.
- Leave in the endotracheal tube and leave a drip up.

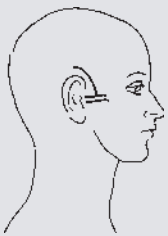


Fig. 9.8 Incision.

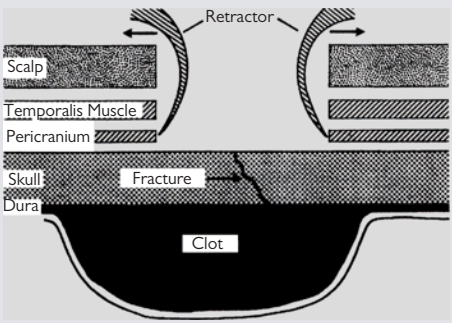


Fig. 9.9 Scrape pericranium.

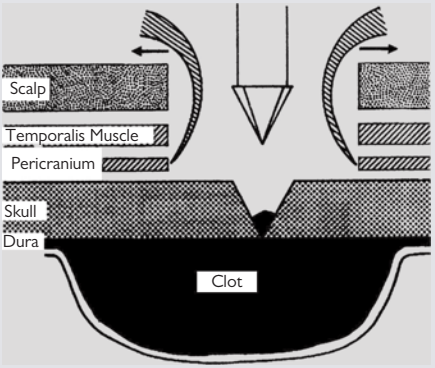


Fig. 9.10 Perforate bone.

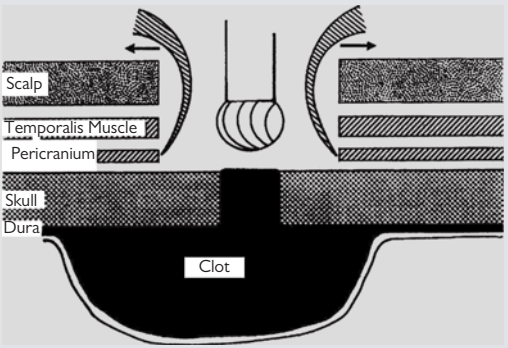


Fig. 9.11 Enlarge perforation.

Extradural haematoma

An arterial bleed that normally results from a skull fracture after head injury (e.g. assault, road traffic accident). Haematomas enlarge rapidly and, unless evacuated equally rapidly, there is high risk of brain herniation and patient death. There is often a lucid interval between initial head injury and subsequent deterioration. Suspect when conscious level ↓ in patient with head injury. Unilateral dilation of pupil, which is sluggish or unresponsive to light, is ipsilateral to side of haemorrhage.

Management

Do a CT scan, if possible, to localize the expanding lesion. Further management depends on the distance to a neurosurgeon. If close, give mannitol before transferring the patient. If the neurosurgeon is remote, a burr hole will be required to prevent brain herniation (Box 9.18, p. 420). In this situation, unless a burr hole is done rapidly, the patient will die or suffer brain damage. You and the patient have nothing to lose, and everything to gain. An inelegant burr hole now will do much more good than an elegant operation 1h or more later.

Blackouts/syncope

The most common causes of blackouts are epilepsy and syncope. A detailed history including any prodromal symptoms (e.g. palpitations, chest pain, dyspnoea, neurological symptoms), and a reliable eyewitness account are helpful in distinguishing the cause.

Syncope

- Brief loss of consciousness due to an acute reduction in cerebral blood flow.
- Most common cause of recurrent episodes of disturbed consciousness and may be precipitated by anxiety or pain. It is due to ↓ venous return to the heart → ↓ cardiac output, or an inadequate response of the heart when ↑ demand requires ↑ cardiac output.
- Causes include ↓ BP (including postural hypotension), vagal slowing of the heart (vasovagal syncope), autonomic neuropathy, dysrhythmias (check electrolytes including Ca^{2+} and Mg^{2+}), aortic stenosis (may occur on exertion—'effort syncope'), hypoglycaemia, hypoxia, carotid-sinus syndrome, hyperventilation, cough syncope, micturition syncope, vertebrobasilar ischaemia (vertebrobasilar TIAs, although most TIAs do not cause syncope), hysteria.

Space-occupying lesions

Classically present with focal neurological signs, ↑ ICP, or seizures. Focal signs may help localize the mass but beware of false localizing signs due to ↑ ICP (➲ p. 390). Causes include the following (see ➲ Focal neurology: space-occupying lesions, p. 110 for causes of SOL in HIV):

- *Infection*: tuberculoma, toxoplasmosis, cysticercosis, echinococcosis, bacterial or amoebic brain abscess, paragonimiasis, schistosomiasis, fungal granulomata.
- *Tumour*: glioma, meningioma, metastases, lymphoma, pituitary adenoma, cysts.
- *Others*: aneurysm, haematoma.

Brain abscess

May occur due to spread from a contiguous focus (e.g. meningitis, subdural empyema) or septic emboli. Often polymicrobial (e.g. streptococci, *Staphylococcus aureus*, anaerobes). Contrast CT brain shows ring-enhancing lesion(s). Give empiric antimicrobial therapy to cover most likely pathogens based on 1° infection site. For 1° brain abscess, ceftriaxone + metronidazole +/− vancomycin is a reasonable regimen. Surgical drainage is indicated for abscesses >3cm diameter.

Hydrocephalus

In older children and adults, the skull will not expand if ↑ ICP. Blockage of CSF flow through the ventricles or failure to reabsorb CSF → ↑ ICP or hydrocephalus. While producing ↑ head circumference in young children, it → ↑ ICP with dilatation of the ventricular system in older persons that will need urgent management. It exists in two forms:

- *Non-communicating hydrocephalus*: due to blockage of CSF flow through the ventricles, normally at foramina or aqueduct between ventricles and/or basal cistern. Caused by any SOL, such as tumour or cyst, or stenosis of the aqueduct. Location of blockage must be identified and blockage removed surgically, or a ventriculoperitoneal shunt placed to relieve pressure.
- *Communicating hydrocephalus*: due to CSF obstruction in basal cisterns or subarachnoid space (CSF still flows out of ventricular system, but it cannot be reabsorbed in arachnoid villi). It may result from intracranial haemorrhage or meningitis (acute pyogenic or chronic meningitis, especially TB or cryptococcal meningitis); cause is often unknown. It may present with a triad of dementia, incontinence, and gait disturbance (this condition is also called normal pressure hydrocephalus). Treatment of any underlying cause with repeated LPs may be sufficient. Medical therapy with a combination of furosemide (adults 40mg, children 1mg/kg daily) and acetazolamide (adults 10–20mg/kg, children 30–50mg/kg daily) has also been recommended as an option for initial treatment in communicating hydrocephalus complicating TBM. Shunting may be required.

Epilepsy

Epilepsy is the continuing tendency to have seizures—spontaneous paroxysmal discharges of neurons that result in clinical symptoms. It is common, affecting 50 million people worldwide, most of whom live in the developing world: 1–2% of the population has epilepsy due to higher incidence of brain injury and CNS infections. It is associated with considerable stigma, ↓ education and employment opportunities, and ↑ mortality. <50% of cases are treated adequately and many people suffer unnecessarily in resource poor settings. There is a need in the developing world to ↓ its incidence (by ↓ the number of head injuries and infections and improving obstetric services) and to provide affordable effective antiepileptic drugs.

Epilepsy

Defined as at least two unprovoked seizures; needs to be distinguished from acute symptomatic seizures, which do not need long-term antiepileptic drugs. A single seizure with a high chance of recurrence (indicated by abnormal electroencephalography (EEG) or neuroimaging) should also be considered as epilepsy, and treatment started.

Acute symptomatic seizures

These occur during or after an acute CNS illness: metabolic, toxic, structural, infectious, or inflammatory. The cause of these seizures is identifiable, e.g. CNS infections, head trauma, eclampsia (urgent delivery is required), and alcohol (particularly withdrawal).

Febrile convulsions

Seizures that occur in children aged 6mths–6yrs in response to an extracranial infection. They have a better prognosis than seizures described earlier in this topic (➲ Febrile convulsions, p. 16).

Causes of epilepsy

No cause is identified in ~70% of cases (some may be due to hamartomas—very small areas of focal dysgenesis). Among the remaining ~30%, causes include:

- *Infection*: encephalitis, cysticercosis, tuberculoma, schistosomiasis, paragonimiasis, sparganosis, hydatid disease, toxoplasmosis, toxocariasis, cerebral malaria, cerebral amoebiasis, neurosyphilis, HIV. Epilepsy can also be a late consequence of almost any meningeal or brain infection.
- *Brain injury*: including antenatal or perinatal brain injury and head injury (e.g. assault or road traffic accident).
- *Other*: incl. brain tumour, metastases, cerebrovascular disease, metabolic causes (especially ↓ Na^+), degenerative disorders, inherited diseases, and drugs.

Clinical features and classification of seizures

Definition is based on origin and spread of seizure. This is important for deciding on further investigations and choice of drug therapy (➲ Management, p. 429; Box 9.19). Classification usually based upon description of seizure (if a history is available), although EEG can help detect focal seizures and epileptic syndromes. Seizures are classified by three key features:

- Where seizures begin in the brain.
- Level of awareness during a seizure.
- Other features of seizures.

Where the seizures begin

- *Focal (partial) seizures*: remain localized to their area of origin, and have signs and symptoms referable to a part of one hemisphere. *Generalized seizures*: originate in centrally positioned cells and activate all parts of brain simultaneously → ↓ consciousness. They do not have features that are referable to only one hemisphere.
- *Focal to generalized (secondarily generalized seizures)*: focal seizures that subsequently spread from their region of origin to involve whole brain → ↓ consciousness.
- *Unknown onset*: if the onset of a seizure is not known, the seizure falls into the unknown onset category. Later, the seizure type can be changed if the beginning of a person's seizures becomes clear.

Awareness

Awareness is used instead of consciousness as it is simpler to evaluate.

- Focal aware: if awareness remains intact, even if the person is unable to talk or respond during a seizure, the seizure is a focal aware seizure. This replaces the term simple partial.
- Focal impaired awareness: if awareness is impaired or affected at any time during a seizure, even if a person has a vague idea of what happened, the seizure is a focal impaired awareness. This replaces the term complex partial seizure.
- Awareness unknown: sometimes it's not possible to know if a person is aware or not, e.g. if a person lives alone or has seizures only at night. In this situation, the awareness term may not be used or it would be described as awareness unknown.
- Generalized seizures: since these seizures are all presumed to affect a person's awareness or consciousness, there are no special terms needed to describe awareness in generalized seizures.

Other features of seizures

- *Generalized seizures* include:
  - Generalized motor seizure: the *generalized tonic–clonic seizure* term is used to describe seizures with stiffening (tonic) and jerking (clonic), formerly known as 'grand mal'. Other forms of generalized motor seizures may happen.
  - Generalized non-motor seizure: these are primarily *absence seizures*, classically as 'petit mal' with 3Hz spike and wave discharges, or atypical absences. These seizures involve brief changes in awareness, staring, and some may have automatic or repeated movements like lip-smacking.
- *Focal seizures* include:
  - Focal motor seizure means that some type of movement occurs during the seizure, e.g. twitching, jerking, or stiffening of a body part or automatisms (automatic movements e.g. licking lips, rubbing hands, walking, or running).
  - Focal non-motor seizure has other symptoms that occur first, e.g. changes in sensation, emotions, thinking, or experiences.
  - Myoclonic and akinetic seizures.

Important points to elicit in the history are:
- *Events before the seizure*: an aura or warning, or abnormal behaviour before the attack suggests a focal origin.
- Movement of the head (localizing sign).
- ↓ consciousness (indicates generalized seizure).
- Stiffening (tonic) or jerking (clonic/convulsive).
- Tongue biting and incontinence of urine (rarely faeces).
- Post-ictal confusion, drowsiness, or headache; and failure to remember the onset all suggest diagnosis of a seizure if there is uncertainty.

Management

If the seizure appears to have a focal onset, look for a treatable underlying cause (➲ Causes of epilepsy, p. 426). If available, do CT or, preferably, MRI.

The decision to start treatment should be made in consultation with the patient and their family. This will depend upon the frequency (usually >2 seizures in a year), cultural, educational, and social consequences of having seizures, and cost and availability of drugs. Patients should be warned not to drive and to avoid swimming; discuss occupational hazards, e.g. working at heights, using power tools, cooking on open fires, etc.

First-line drugs
- *Phenobarbital*: first choice for partial and generalized tonic–clonic seizures in low-resource areas since it is widely available. Start at 1–1.5mg/kg po od (30–60mg in adults) building up as required to usual maintenance dose of 2.5–4mg/kg od or bd daily (max. 180mg daily). Side effects in children appear at higher doses.
- *Carbamazepine*: first choice for tonic–clonic seizures in association with partial seizures; reserve drug for partial seizures alone. Start at 100mg po bd, building up to 600mg bd if tolerated (children 5mg/kg up to 20mg/kg/d).
- *Sodium valproate*: first choice for typical absences, myoclonic and akinetic seizures, and tonic–clonic seizures, particularly in association with typical absences. Start at 300mg po bd, building up to 750mg bd (max. = 2.5g/d) as required (children 5mg/kg/d up to 40mg/kg/d). Avoid in women who may fall pregnant.
- *Phenytoin*: reserve drug for tonic–clonic and partial seizures (not for absences). Start at 3–4mg/kg (adults) or 1.5–2.5mg/kg (children) oral od; adjust according to response and plasma levels; usual dose 200–500mg (adults); max. dose in children 300mg daily. It is a toxic drug and plasma levels should ideally be monitored.
- *Other drugs*: include clonazepam, ethosuximide, lamotrigine, and newer drugs (vigabatrin, gabapentin, levetiracetam).

Changing drugs

Persist with one drug until it has been used at its maximum dose or causes intolerable side effects before considering a change. Introduce the new drug at its starting dose and slowly ↑ to its mid-range; then start to slowly ↓ the dose of the old drug.

Stopping drugs

It is unclear how long any person needs to stay on antiepileptic drugs once the seizures have been controlled. In general, if a patient has not had a seizure within the last 2yrs, discuss with them whether they would like to discontinue treatment, balancing the risk of recurrence vs side effects.

Box 9.19 Principles of antiepileptic drug therapy

- Establish a clear clinical diagnosis.
- EEG may help classify the seizures and/or syndrome if available.
- Choose a drug, considering the:
  - Seizure type(s).
  - Interaction with other drugs.
  - Patient's age.
  - Possibility of pregnancy.
  - Price.
- Start with one drug and aim to control seizures with monotherapy.
- Begin with low-modest dosage, ↑ slowly over 2–3mths.
- Give full information to the patient concerning:
  - Names and alternative names of the drug supplied.
  - The main side effects of the drug.
  - The need for adherence with instructions.
  - Possible interactions with other medications.
- Monitor progress, seizure frequency, and side effects.
- Ensure adequate supplies of antiepileptic drugs.

Status epilepticus

Status epilepticus is defined as at least 15min of continuous seizures or >2 discrete seizures without regaining consciousness. Status epilepticus can → death, permanent neurological damage, or the onset of chronic epilepsy. Risk factors for such sequelae incl. aetiology, duration of seizure, and systemic complications.

Aetiology

The most common causes are acute CNS infection (particularly in children), head injury, and known epilepsy. Other causes include pesticide poisoning, stroke, and eclampsia.

Principles of management

- Remove patient from potential danger.
- Stop seizures quickly.
- Prevent complications.
- Find and control the underlying causes.

Management

- Secure the airway, preferably with oral airway, give O_2.
  - *Note*: do not attempt to intubate if the jaw is clenched. Wait for sedation to have its effect.
- Give glucose 20% as 50mL IV bolus unless hypoglycaemia excluded.
- Give thiamine 250mg by slow IV infusion over 20min if patient alcoholic or malnourished: note risk of anaphylaxis.
- Give diazepam 10mg in 2–4mL IV or pr at a rate of 5mg/min (children <12yrs old 0.3–0.4mg/kg, or 1mg per year of age; max. 10mg). This should control >80% of patients. Repeat once after 10min if necessary. Beware respiratory depression following bolus diazepam. Lorazepam or midazolam may be used as alternatives if available.

If convulsions continue after giving diazepam:

- *Manage the patient in ICU if possible.*
- *Give phenytoin* 10–15mg/kg as IV infusion at <50mg/min through a separate giving set. Once seizures are controlled, maintain with phenytoin 100mg po or IV every 6–8h. Alternatively, give phenobarbital 10–20mg/kg as an IV infusion, at <100mg/min to a maximum of 1g. Phenobarbital is preferred for seizures associated with poisoning. Clomethiazole is another alternative. Do not give more diazepam.
- *Beware respiratory depression and hypotension.*
- *Check for and treat* ↑ ICP.

If convulsions continue after phenytoin:

- Exclude pseudo-status (i.e. pseudo-seizures).
- Check drugs have been given correctly.
- Then give general anaesthetic and ventilate, while treating causative condition. Give thiopental 75–125mg (3–5mL of a 2.5% solution) IV over 10–15s. Give further doses according to response. Beware of hypotension. If large amounts of thiopental are infused over a long period, it will accumulate and delay recovery.

Cysticercosis

A common cause of epilepsy worldwide. Humans usually become infected with the pork tapeworm *Taenia solium* by eating cysts in undercooked pork (see life cycle, Fig. 9.12). Accidental ingestion of eggs from human faeces then → cysticercosis in which humans act as alternative host with involvement of CNS, muscles, skin, eyes. Symptoms are caused by acute inflammatory reaction to living and dying parasites (active disease), and chronic inflammatory reaction to cysts—fibrosis, calcification, and granulation (inactive disease).

Clinical features

- CNS involvement (neurocysticercosis) usually presents as epilepsy.
- As number and localization of cysts vary greatly, can also → hydrocephalus, dementia (frontal lobe involvement; often in children).
- Infarcts (due to vasculitis).
- Basal meningitis; cranial nerve defects; spinal symptoms.
- Subcutaneous and muscular cysts (small, round, painless, firm nodules) occur in 25% of CNS cases, but may also occur in isolation.
- Calcified cysts resembling rice grains may be incidental finding on X-ray. Rarely, cardiac involvement can → conduction defects. Ocular cysticercosis may → blurring of vision and the sensation of something in the eye. If untreated, it may → blindness and eye atrophy.

Diagnosis Active CNS lesions can be seen on CT/MRI (Fig. 9.13); calcified inactive lesions can be seen on CT (+/− plain X-ray). Serology.

Management

- Control seizures with anticonvulsants.
- Treat any cerebral oedema (e.g. steroids) or hydrocephalus (shunt).
- Treat active parenchymal cysts with anti-parasite drugs if ICP not ↑:
  - If only 1–2 active cysticerci give albendazole 15mg/kg/d (max. 800mg) oral in two doses for 10–14d.
  - If >2 active cysticerci give albendazole as above-described plus praziquantel 50mg/kg/d oral in three divided doses for 10–14d.
  - Consider repeat anti-parasitic therapy for cystic lesions persisting >6mths after treatment.
- Give adjunctive steroids to all patients on anti-parasitic therapy (e.g. dexamethasone 8mg/d or prednisolone 1–2mg/kg/d for 10–14d, followed by taper).
- Anti-parasitic treatment not required for calcified (inactive) cysts.
- Surgery is usually reserved for subarachnoid and intraventricular cysts causing hydrocephalus or cord compression.
- Ocular infection in isolation should not be treated with drugs. Ocular cysts may need to be treated surgically.

Prevention

Health education and public health measures to improve personal hygiene, meat inspection, adequate cooking of pork, sanitation on farms, and sewage disposal to prevent pigs consuming human faeces. Mass chemotherapy including praziquantel mass treatment for schistosomiasis may also have a role in control at the population level.

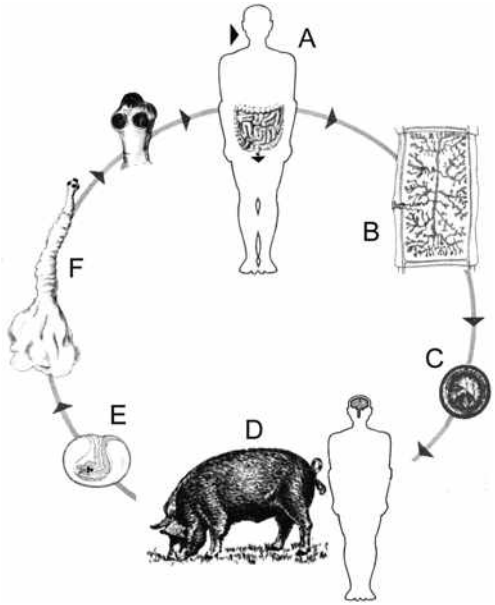


Fig. 9.12 Life cycle of *Taenia solium*. Humans (A) are the definitive host, with a tapeworm 3–4m long in the small intestine. Proglottids (segments; B) of the tapeworm detach and are shed in the faeces, each containing a branching uterus and thousands of eggs (C). When human faeces are ingested by humans or pigs (D) these eggs, which contain an embryo, develop into a larval stage (the cysticercus, E) in muscles, brain, or other tissues. When a human ingests uncooked pork containing cysticerci, these evaginate (F) in the human small intestine to form the head of the tapeworm; this elongates and forms new segments, completing the life cycle.

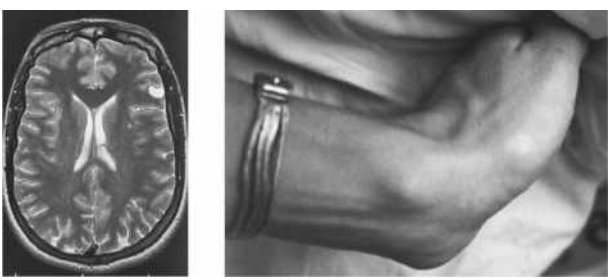


Fig. 9.13 MRI of cysticercus in left fronto-parietal cortex of a 35yr-old woman who presented with focal seizures. A cysterícus was also visible under the skin of her left wrist. Both lesions disappeared after 4wks of albendazole treatment.

Weak legs and spinal cord disease

Causes of weak legs include upper motor neurone (UMN) and lower motor neurone (LMN) pathology (Box 9.20). There may be mixed UMN and LMN signs in some conditions (e.g. spinal cord compression accompanied by nerve root compression; conus medullaris lesions; motor neurone disease). A careful history and examination will suggest the most likely anatomical location and differential diagnosis. It is important to establish:

- Is the weakness bilateral (= paraparesis) or unilateral?
- Was the onset gradual or sudden?
- Is the tone ↑ (suggesting UMN pathology) or ↓ (suggesting LMN pathology)?
- Is there sensory loss? A sensory level is a strong clue to a spinal cord disease.
- Is there any loss of sphincter control (bowels or bladder)?
- Is there normal sensation around the sacrum and good anal tone?

The differential diagnosis then depends on the presentation:

Sudden weak legs with spasticity

Cord compression—a medical emergency

- Consider especially if rapidly progressive leg weakness and/or sphincter failure. Causes include:
  - Spinal/paraspinal infection (e.g. TB, *Brucella*, pyogenic abscess, schistosomiasis, cysticercosis).
  - Tumours (metastases, lymphoma, myeloma).
  - Disc prolapse.
  - Vertebral collapse 2° avascular necrosis in sickle cell disease.
  - Paget's disease.
  - Trauma.
- Image spine (X-ray and/or CT/MRI if available).
- Treat cause.
- If malignancy, give steroids immediately (e.g. dexamethasone 8mg bd IV) and consider surgery, radiotherapy, chemotherapy.
- Drain epidural abscesses (send for bacterial and TB culture if available); treat with empiric antibiotics according to suspected aetiology.
- Early intervention ↓ risk and severity of longer-term neurological sequelae due to spinal cord compression.

Transverse myelitis

- Symptoms include back pain, fever, double incontinence, sensory loss at defined level often with surrounding zone of hyperaesthesia.
- Usually infectious/postinfectious—associated infections include herpesviruses, *Mycoplasma*, *Listeria*, *Borrelia*, syphilis, HTLV-1, HIV, West Nile virus, Zika virus.
- Multiple sclerosis is less common in the tropics.

Cord infarction

Vasculitis, anterior spinal artery thrombosis, trauma, compression, dissecting aortic aneurysm, surgery; tumours.

Box 9.20 Causes of weak legs

Upper motor neurone causes

- Spinal cord pathology (extrinsic compression or intrinsic disease).
- Brainstem pathology.
- Cortical disease (*note*: stroke usually causes unilateral weakness).
- Parasagittal meningioma (rare).

Lower motor neurone causes

- Radiculopathy (nerve root pathology due to extrinsic compression or intrinsic disease).
- Cauda equina syndrome.
- Peripheral neuropathy.

Acute flaccid paralysis

See Table 9.5 for comparison of conditions in the differential diagnosis of acute flaccid paralysis. Causes include:

- *Cauda equina compression*—a neurosurgical emergency: ask about back and radicular leg pain, bladder and bowel sphincter control. Check perineal area for loss of sensation (saddle anaesthesia). Do pr to assess anal sphincter tone. Causes include tumour; disc prolapse; canal stenosis; TB; cysticercosis; schistosomiasis. Management is similar to spinal cord compression (➔ p. 433)—focus on treating the cause.
- Poliomyelitis (➔ Poliomyelitis, p. 437).
- GBS (➔ Guillain–Barré syndrome, p. 436).
- *Other*:
  - Acute cord trauma/infarction.
  - Myelitis (in early stages).
  - Rabies (➔ Rabies, p. 404).
  - Lumbosacral nerve lesion; hypokalaemic periodic paralysis.

Chronic spastic paraparesis/weak legs

- *Cord compression*: spinal degenerative disease (e.g. cervical spondylosis); many of the causes of acute spastic paraparesis (➔ p. 433).
- *Human T lymphotropic virus (HTLV-1)*-associated myelopathy/tropical spastic paraparesis (HAM/TSP)—progressive spastic paraparesis. Usually presents in middle age. Described in several regions including Caribbean, Japan, equatorial Africa, South America.
- Subacute combined degeneration of the cord (Box 9.21; ➔ Vitamin B_{12} deficiency, p. 446).
- *Konzo*: myelopathy due to chronic cyanide consumption in cassava.
- *Lathyrism*: due to excessive grass pea consumption (e.g. in India).
- *Other causes*:
  - Motor neurone disease (often mixed UMN/LMN signs, but no sensory loss).
  - Syphilitic taboparesis (mixed UMN/LMN signs and sensory loss).
  - Syringomyelia.
  - Intrinsic cord tumours.

Chronic flaccid paraparesis/weak legs

- *Peripheral neuropathies and myopathies*: check for arm involvement.
- *Tabes dorsalis*: see section on tertiary syphilis (➔ Syphilis, p. 612).

Box 9.21 Causes of absent knee jerks with extensor plantar responses

- Friedreich's ataxia.
- Motor neurone disease.
- Subacute combined degeneration of the cord.
- DM.
- Syphilis.

Principles of management of paraplegia

- Emergency management of acute spinal cord or cauda equina compression (if applicable): imaging, consider surgical decompression, +/− steroids.
- Prevention of pressure sores by turning every 2h.
- Attention to bladder and bowels (urinary catheter if incontinent).
- Ensure adequate hydration and nutrition.
- Prevent complications: aspiration and pneumonia (ensure adequate swallowing), DVT (support stockings/heparin), contractures (physiotherapy), malaria (mosquito net).
- Identify and treat the underlying cause.

Guillain–Barré syndrome

GBS is an acute polyradiculitis that symmetrically affects the spinal nerve roots and often the cranial nerve roots as well. GBS may be a consequence of preceding infection but in 60% of cases no cause is identified. *Campylobacter jejuni* is the most commonly identified antecedent infection; other infectious causes include Zika virus, EBV, *Mycoplasma pneumonia*, herpes zoster, Lyme disease, and diphtheria, usually preceding the onset of GBS by 1–2wks. GBS develops over a few hours (rarely), to several weeks, and is a medical emergency. Respiratory arrest may occur without notice in severe cases; sudden death may also be caused by the cardiovascular consequences of autonomic nervous system involvement. GBS patients need constant observation, in an ICU if possible.

Clinical features

Usually ascending weakness, which includes progressive symmetrical limb weakness of <4wks' duration; distal paraesthesia (less often sensory loss) usually with total absence of deep tendon reflexes. Back and limb pain may be occasionally present. Also cranial nerve palsies (particularly VII); autonomic nervous system disturbances; ileus.

Management

Prognosis for spontaneous recovery is good. Treatment generally limited to supportive nursing care and prevention of complications. Monitor respiratory function and heart rhythm. Cases with rapid progression and respiratory insufficiency should be treated with plasma exchange or high-dose immunoglobulin 0.4g/kg on 5 successive days, if available; this ↓ hospital stay. Corticosteroids provide no benefit. Recovery occurs over several weeks or months with remyelination of peripheral nerves.

Poliomyelitis (polio)

This disease, usually of young children, is caused by the poliovirus, an enterovirus. The virus selectively infects and destroys anterior horn cells in the spinal cord → acute flaccid paralysis, the cardinal sign of polio. The clinical disease is relatively uncommon, however: 99% of infected people show no paralytic manifestations.

Epidemiology

A global effort is under way to eradicate polio by high immunization coverage, effective surveillance, and a rapid, vigorous response to new cases. As a result, global polio incidence has ↓ by >99% from 350,000 cases in 1988 to 33 cases in 2018. and it remains endemic in only three countries: Afghanistan, Nigeria, and Pakistan.

Transmission Via ingestion of faecally contaminated food or water, or via droplet spread from the respiratory tract.

Clinical features

Polio and other conditions in the WHO differential diagnosis of acute flaccid paralysis are summarized in Table 9.5. Prodromal symptoms of polio are common to many infections and practically indistinguishable: fever, malaise, headache, drowsiness, sore throat. In a minority, CNS disease (pre-paralytic disease) follows with abrupt onset of fever, headache, body pains, sensory disturbances, and neck stiffness, due to poliovirus meningitis. Flaccid paralysis then occurs in 65%, developing asymmetrically over a variable time, particularly affecting lower limbs with no sensory loss (although pain is characteristic). The paralysis rarely progresses for >3d or after the temperature falls. There is then some recovery of function over the following weeks or months, as some damaged anterior horn cells recover. Death is relatively uncommon, but results from aspiration or airway obstruction (bulbar paralysis) or respiratory failure (respiratory paralysis). A rare complication is slow deterioration of function after many years—the post-polio syndrome.

Diagnosis Clinical, with retrospective serological analysis. Isolation of wild poliovirus from the stools confirms a case.

Management

Supportive (Box 9.22). Paralytic polio is made worse by IM injections (e.g. of antibiotics) during pre-paralytic phase or by muscles becoming fatigued (e.g. after exercise), so a high index of suspicion in endemic regions is important to prevent polio being made worse. Avoid injections. Bed rest essential. Give analgesia, sedation. Patients must be carefully observed during onset of paralysis for signs of life-threatening bulbar and respiratory paralysis. Nurse patients with poor swallowing on their side. Good nursing care, including frequent suction and observations, may delay need for a tracheostomy. However, perform a tracheostomy early in serious cases.

Prevention Vaccination; improved sanitation, hygiene, and water supply.

Box 9.22 Polio rehabilitation

Acute stage

- *Treatment*: based on rest and positioning.
- Support the wrist and hands (if affected) in a functional position with a splint or other support (e.g. pillow).
- Support the ankle (if affected) at 90° and avoid excessive inversion or eversion.

Subacute stage

- Progress from passive movements → active assisted movements → active movements within the normal range.
- Progress → standing and walking with assistance—use walking aids if necessary (e.g. stick, crutches).
- Avoid:
  - Muscle shortening.
  - Malformation due to muscle imbalance.

Table 9.5 WHO differential diagnosis of acute flaccid paralysis

	Polio	Guillain–Barré syndrome	Traumatic neuritis	Transverse myelitis
Onset of paralysis	24–48h, from onset to full paralysis	Hours to 10d	Hours to 4d	Hours to 4d
Flaccid paralysis	Usually acute, asymmetrical, principally proximal	Usually acute, symmetrical, and distal	Asymmetrical, acute, affecting one limb only	Acute, affecting lower limbs, symmetrical
Muscle tone	Reduced or absent in the affected limb	Global hypotonia	Reduced or absent in the affected limb	Hypotonia in lower limbs
Deep tendon reflexes	Decreased to absent	Globally absent	Decreased to absent	Absent in lower limbs early, increased late
Sensation	Severe myalgia, backache, no sensory changes	Cramps, tingling, hypo anaesthesia of palms/soles	Pain in gluteus muscles, hypothermia	Anaesthesia of lower limbs, sensory level
Cranial nerve	Only when bulbar involvement is present	Often present, affecting nerves VII, IX, X, XI, XII	Absent	Absent
Respiratory insufficiency	Only when bulbar involvement is present	In severe cases; worsened by bacterial pneumonia	Absent	Sometimes
CSF findings	Inflammatory	Albumin-cells dissociation	Normal	Normal or a few cells
Bladder dysfunction	Absent	Transient	Never	Present

Peripheral neuropathy

Peripheral neuropathy may affect individual peripheral or cranial nerves (mononeuropathies), or multiple nerves (polyneuropathies). Involvement of multiple individual nerves simultaneously is termed 'mononeuritis multiplex'.

Mononeuropathies

May arise from trauma (e.g. fractured fibula → common peroneal nerve palsy), compression (e.g. median nerve in carpal tunnel syndrome), diabetes, or leprosy. Diabetes and leprosy may also → mononeuritis multiplex or widespread peripheral polyneuropathy.

Polyneuropathies

Usually affect the peripheries initially (the longest nerves are the most vulnerable to damage), producing a symmetrical glove-and-stocking distribution. In the tropics, environmental toxins and nutritional deficiencies are important causes (Box 9.23). They may be seen in epidemic form after toxins are released into the environment by industry or in an endemic form in particular regions. Some toxins are used in traditional medicines or they may contaminate food, liquor, etc. They frequently produce a recognizable syndrome. As always, there is no replacement for local clinical experience. In these situations, treatment involves removal of the toxin and/or supplementation with the deficient nutrient. The effects of many neuropathies are permanent.

Causes of unilateral foot drop

Common peroneal nerve palsy (Box 9.23), stroke, prolapsed vertebral disc, motor neurone disease, organophosphate poisoning, idiopathic.

Box 9.23 Causes of polyneuropathy

- *Vitamin and micronutrient deficiencies*: vitamins B_1, B_6, and B_{12}; variety of multiple nutrient deficiencies (➲ Chapter 16).
- *Toxins*:
  - *Heavy metals*—including lead (motor involvement), thallium (found in rodenticides → alopecia), arsenic (Mee's nail lines, changes in skin pigmentation, skin cancers).
  - *Drugs*—including isoniazid, ethambutol (affects optic nerve), sulfonamides, clioquinol, metronidazole, phenytoin, didanosine, stavudine.
  - *Industrial chemicals/solvents*—e.g. triorthocresyl phosphate.
  - *Pesticides*, particularly organophosphorous compounds.
  - *Excessive consumption of certain foods* (e.g. cassava containing a cyanogenic glycoside) can cause tropical ataxic neuropathy.
- *Metabolic diseases*: DM, renal/liver failure, alcohol, hypothyroidism.
- *Infections*: leprosy, HIV, syphilis.
- *Other*: genetic diseases, malignancy, connective tissue disease.

Leprosy

Leprosy (Hansen's disease) still elicits immense stigma in many communities. It is a chronic inflammatory disease affecting skin and peripheral nerves caused by *Mycobacterium leprae*. Presentation and progress are determined by the host cell-mediated immune response to the mycobacterium. Most people (>95%) develop an effective immune response and clear *M. leprae*. A minority are unable to do so and develop clinical leprosy. The clinical features then form a spectrum determined by the immune response, from tuberculoid (TT) to lepromatous (LL) leprosy (Table 9.6). At the TT pole there is a strong immune response to the bacteria that limits bacillary growth (TT is paucibacillary), but damages peripheral nerves and skin. At the LL pole, there is cellular anergy towards *M. leprae* with abundant bacillary multiplication (LL is multibacillary); see Clour Plate 10b. Between these two poles are the borderline patients—borderline tuberculoid (BT), borderline (BB), and borderline lepromatous (BL)—reflecting the spectrum of immune response and bacterial load. The polar groups (TT, LL) are stable, but the borderline groups are unstable and experience tissue-damaging reactions. The immune-mediated reactions that complicate leprosy are difficult to manage and require immune-suppression.

Transmission

Untreated lepromatous patients discharge bacilli from the nose. Infection occurs when *M. leprae* invades via the nasal mucosa with haematogenous spread → skin and nerve. Leprosy bacilli can survive for several days in the environment. People in close contact with infected people have a greater, but still small, chance of becoming infected. The incubation period is 2–5yrs for TT cases and 8–12yrs for LL cases. HIV infection does not appear a risk factor for the development of leprosy.

Clinical features

- *Skin*: most common lesions are anaesthetic macules or plaques; more rarely, papules and nodules, or diffuse infiltration. Indeterminate leprosy is an early form of disease often found in screening programmes; lesions can last for months before resolving or progressing to established leprosy.
- *Nerve enlargement and damage*: occurs in peripheral nerve trunks (e.g. great auricular nerve (neck), ulnar nerve (elbow), radial-cutaneous nerve (wrist), median nerve (wrist), lateral popliteal nerve (neck of the fibula), and posterior tibial nerve (medial malleolus)), producing typical patterns of regional sensory and motor loss (see Colour Plate 11). Small dermal nerves also involved, producing patches of anaesthesia in TT/BT lesions, and glove and stocking sensory loss in LL patients.
- *Other organ involvement*: eyes (may → blindness); bones (dactylitis, resorption); testes (orchitis, sterility); nasopharynx (nasal collapse).

Clinical presentations

Include skin lesions, weakness, and/or numbness due to peripheral neuropathy, or a burn/ulcer in an anaesthetic hand or foot. Borderline patients may present in reaction with nerve pain, sudden palsy, multiple new skin lesions, pain in the eye, or systemic febrile illness. The ulceration and digit loss seen in leprosy is due to 2° damage in neuropathic hands and feet and is not an intrinsic disease feature.

Diagnosis

Leprosy is present when one of three features is detected:

- A typical skin lesion (loss of sensation in TT/BT patients).
- Thickened peripheral nerves.
- Skin smear from lesion edge/ear lobe positive for mycobacteria.

Test skin lesions for sensation. Palpate peripheral nerves to assess enlargement/tenderness. Assess nerve function by testing the small muscles' power and sensation in hands/feet. Many patients are unaware of their anaesthesia. Eye function should be checked (visual acuity, corneal sensation, and eyelid closure). Serology is not helpful.

Table 9.6 Clinical features of leprosy

Classification	Skin lesions	Nerve involvement
Indeterminate	Solitary hypopigmented 2–5cm lesion. Centre may show sensory loss although both doctor and patient are often uncertain about this loss. May become TT-like	None clinically detectable
TT	Lesions with well-defined borders and anaesthesia. The patch is dry (loss of sweating) and hairless	May have one peripheral nerve affected. Occasionally presents as a mononeuropathy
BT	Irregular plaques with raised edges and anaesthesia. Satellite lesions at the edges	Asymmetrical peripheral nerve involvement
BB	Many lesions with punched out edges. Satellites are common	Widespread nerve enlargement. Sensory and motor loss
BL	Many lesions with diffuse borders and variable anaesthesia	As above
LL	Numerous nodular skin lesions in a symmetrical distribution. Lesions are not dry or anaesthetic. There are often thickened shiny earlobes, loss of eyebrows, and skin thickening	As above

Management of leprosy

Chemotherapy to treat the infection

WHO regimens combine monthly supervised drug treatment with daily self-administration of an additional drug(s) (Table 9.7). More than 16 million people have been treated with these regimens. Relapse rates are 0.1%/yr. Clinical improvement is rapid and adverse reactions are rare. These drugs are considered safe during pregnancy and breastfeeding. Patients are classified for treatment by the number of skin lesions present: paucibacillary have 1–5; multibacillary >5.

Educate the patient about leprosy

Within 72h of starting chemotherapy, they are non-infectious and can lead a normal social life. No limitations on touching, sex, sharing utensils. Leprosy is not a curse from God or a punishment. Gross deformities are not inevitable endpoint of disease. Care and awareness of limbs are as important as chemotherapy.

Prevent disability

Monitor sensation and muscle power in patient's hands, feet, and eyes as part of routine follow-up, so that new nerve damage is detected early. Treat any new damage with prednisolone 40mg daily, reducing by 5mg/d each month. Patient self-awareness is crucial in minimizing damage. Patients with anaesthetic hands or feet need to inspect hands and feet (using a mirror) daily for injuries or infection and dress wounds immediately. Protect hands and feet from trauma ('trainers' are excellent shoes for anaesthetic feet). Identify the cause of any injury so that it can be avoided. Soak dry hands and feet in water and then rub with oil to keep skin moist.

Manage complications

Ulcers in anaesthetic feet are the most common cause of hospitalization. Ulceration is treated by rest and cleaning. Ulcers should be carefully probed to detect osteomyelitis and sinuses that require surgical debridement. Unlike ulcers in diabetic or ischaemic feet, ulcers in leprosy heal if they are protected from weight-bearing. No weight-bearing is permitted until ulcer heals. Ensure appropriate footwear to prevent recurrence.

Support the patient socially and psychologically.

Reactions

Immune-mediated, tissue-damaging phenomena that may occur before, during, or after treatment. Reactions are important because they are common, recurrent, and require prompt treatment to prevent serious nerve damage. Presentation and management of reactions are summarized in Box 9.24. Do not stop chemotherapy during a reaction. Patients with difficult reactions should be discussed with an expert in leprosy (e.g. regional government leprosy officers, international leprosy non-governmental organizations (NGOs)).

Table 9.7 WHO recommended multi-drug therapy regimens

Leprosy type	Drug treatment		Duration
	Monthly supervised	Daily self-administered	
Paucibacillary (1–5 skin lesions)	Rifampicin 600mg	Dapsone 100mg	6mths
Multibacillary (>5 skin lesions)	Rifampicin 600mg + clofazimine 300mg	Dapsone 100mg + clofazimine 50mg	12mths

Box 9.24 Reversal reaction (type 1 reaction)

Due to delayed type hypersensitivity; occurs in 30% with borderline leprosy. Skin lesions become erythematous; peripheral nerves become tender and painful. Loss of nerve function can be sudden, with foot-drop occurring overnight. Neuritis may occur without skin lesions or in a clinically silent form without nerve tenderness.

Management

For severe reactions, prednisolone 40–60mg po od reduced every 2–4wks over 20wks. A few patients may require 15–20mg prednisolone daily for many months. Response rates vary depending on the severity of initial damage, but even promptly treated nerve damage will only improve in 60% of cases.

Erythema nodosum leprosum (ENL) (type 2 reaction)

This is due to immune complex deposition and occurs in 20% of LL and 5% of BL patients. It manifests with malaise, fever, and crops of painful red nodules that become purple and then resolve. If severe, plaques may form with necrosis and ulceration. Iritis is common; other signs are bone pain and swollen joints, painful neuritis, lymphadenopathy, iridocyclitis, orchitis, nephritis (rarely).

Management

In moderate and severe cases (systemic features or painful nerves), treat in hospital with one of:

- Prednisolone 40–60mg po od, reduced after 2wks by 5–10mg every 2wks (best for short episodes).
- Thalidomide 400mg nightly for 4wks. Once satisfactory response, ↓ by 50mg every 2–4wks (best drug, but contraindicated in women of childbearing age and often not available; causes drowsiness).
- Clofazimine 300mg daily, reduced after 3mths (preferred drug for premenopausal women; takes 3–4wks to have full effect so combine with prednisolone initially). Causes brown skin staining.
- Treat iridocyclitis with steroid and homatropine eye drops.

ENL is difficult to treat. Some patients develop a chronic relapsing form, which may last for up to 5yrs, but will then resolve.

Dementia

Unlike confusional states and delirium, there is no disturbance of consciousness in dementia. It is a chronic or progressive condition characterized by ↓ higher mental function (e.g. memory, reasoning, comprehension), and emotional and behavioural changes. Common causes are Alzheimer's disease and multiple strokes (vascular dementia). Uncommon, but treatable causes include communicating hydrocephalus; vitamin B_{12} or B_1 deficiency; hypothyroidism; syphilis; neurocysticercosis; brain tumour; chronic subdural haematoma. HIV can cause a dementia that is variably responsive to antiretroviral therapy (➲ Antiretroviral therapy, p. 81).

Management

Identify the few patients with treatable causes. Aim to supply others with general support to give highest quality of life possible.[2]

Remember that the family will also need support. Information useful to Alzheimer's disease patients and their carers is available at http://www.alz.org.

2 Guidance on dementia assessment and management is given in: World Health Organization (2016). mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP). Version 2. Geneva: World Health Organization. Available free from: https://www.who.int/publications/i/item/9789241549790

Chapter 10

Haematology

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Anaemia

Introduction

Anaemia (Table 10.1) affects ~40–70% of children and pregnant women in resource-poor countries. Children <5yrs old bear the largest burden globally. A slight ↓ in Hb is a physiological response to pregnancy, due to an ↑ in the plasma: red blood cell (RBC) ratio. Anaemia in pregnancy is associated with 25–40% of maternal deaths.

Causes of anaemia

Anaemia is due to ↓ RBC production or ↑ RBC loss/haemolysis (Tables 10.2 and 10.3); more than one cause may be present. Younger RBCs (reticulocytes) appear 'bluer' on a blood film → polychromasia. Reticulocytes ↑ if RBC consumption/loss and ↓ if RBC production is impaired. The blood film morphology, degree of reticulocytosis, and the size of RBCs (i.e. mean cell volume (MCV)) are helpful in determining the cause (➲ Box 10.2, p. 450).

Severe anaemia is usually multifactorial. Infections (HIV, bacteraemia, malaria, hookworm), nutritional deficiency (folate, iron, vitamins B_{12} and A), and blood loss are common associated causes of severe anaemia.

Table 10.1 WHO definitions of anaemia

Age	Hb (g/dL)
6–59mths	<11.0
5–11yrs	<11.5
12–13yrs	<12.0
Non-pregnant women	<12.0
Pregnant women	<11.0
Men	<13.0

Table 10.2 Causes of anaemia due to ↓ RBC production

Aetiology	Clinical findings	Laboratory tests
Iron, folate, and vitamin B_{12} deficiency		
Iron	Koilonychia, angular stomatitis, oesophageal webs	↓ MCV, MCH, MCHC, RBC count, ferritin, serum Fe, transferrin saturation; ↑ TIBC Blood film: microcytic, hypochromic RBCs, pencil cells
Folate and vitamin B_{12}	Glossitis, ↑ skin pigmentation, subacute combined degeneration of the cord (vitamin B_{12} only)	↓ platelets ↓ WCC, ↑ MCV, MCH; normal MCHC. Blood film: oval macrocytes, hypersegmented neutrophils

Aetiology	Clinical findings	Laboratory tests
↓ erythropoietin		
Renal failure		Normocytic anaemia Blood film: 'burr cells'
Anaemia of chronic inflammation		
	Features specific to the underlying condition	Normo/microcytic anaemia, ↓ serum Fe, TIBC; ↓/normal transferrin saturation/normal ferritin
Bone marrow suppression or dysfunction		
Drugs (e.g. cytotoxics), aplastic anaemia, malignant infiltration, alcoholism, hypothyroidism, myelodysplasia	Features specific to underlying condition	↓ platelets and WBC normal/↑ MCV

MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; TIBC, total iron-binding capacity.

Table 10.3 Causes of anaemia due to ↑ RBC loss and haemolysis

Aetiology	Clinical findings	Laboratory tests
↑ RBC loss		↑ reticulocyte count, polychromasia (unless acute)
Haemorrhage		
Acute (e.g. postpartum, trauma)	Shock (tachycardia, hypotension, cold extremities)	MCV normal, Hb, and HCT initially normal
Chronic, (e.g. peptic ulcer, hookworm, schistosomiasis)	Melaena, haematuria	Fe deficiency, ↑ platelets, stool/urine for parasites
Haemolytic anaemias	Jaundice, dark urine	↑ bilirubin (unconjugated) and LDH
Inherited		
Haemoglobinopathies, e.g. sickle cell disease, thalassaemia	FHx anaemia, ↓ growth, hepatosplenomegaly, gallstones, leg ulcers	Blood film, haemoglobin electrophoresis, HPLC

Aetiology	Clinical findings	Laboratory tests
Enzymopathies, e.g. G6PD deficiency	FHx, gallstones, infection or recent drug ingestion	Intravascular haemolysis, e.g. ↓ haptoglobins, haemoglobinuria, haemosiderinuria Blood film: Bite/ghost cells (G6PD), basophilic stippling (pyrimidine 5' nucleotidase deficiency)
Membranopathy, e.g. hereditary spherocytosis	FHx, splenomegaly, gallstones	Extravascular haemolysis (↑ conjugated bilirubin, urobilinogen); blood film (spherocytes)
Acquired: immune		
Alloimmune, e.g. post transfusion, haemolytic disease of the newborn	Transfusion <10d	Blood film (spherocytes), +ve direct Coombs' test RBC antibodies
Autoimmune, e.g. antibody mediated, drug induced	Underlying infection, lymphoma, autoimmune disease, discoloured extremities (cold antibody)	Blood film (spherocytes), +ve direct Coombs test, RBC antibodies, RBC agglutination (cold antibodies)
Acquired: non-immune		
Infections, e.g. malaria, bartonellosis, parvovirus B19, clostridial sepsis	Underlying infection	Blood film (malaria, bartonella)
Others, e.g. microangiopathic haemolysis, burns, snake bite		Blood film (RBC fragmentation), thrombocytopenia, renal failure

FHx, family history; HCT, haematocrit; HPLC, high-performance liquid chromatography.

Clinical features of anaemia

History

Symptoms of anaemia depend on the rapidity of onset and severity. Chronic anaemia may be asymptomatic because of a compensatory ↑ in cardiac output. Symptoms are usually non-specific: fatigue, headache, dizziness, syncope, dyspnoea, palpitations, ↓ work or intellectual capacity. Anaemia may also ↑ pre-existing intermittent claudication or angina.

The history is important in determining the cause(s) of anaemia:

- Previous history and FHx of anaemia suggests an inherited disorder, e.g. haemoglobinopathy or G6PD deficiency.
- Haemolysis may be suggested by splenomegaly, jaundice, and dark urine, and may be precipitated by infections.
- Blood loss can be revealed from colour of stools, haematuria, and menstrual history. Ask about recent surgery, childbirth, or trauma.
- Occupation may be important, e.g. fishermen may be prone to schistosomiasis and rice farmers to hookworm infection.
- Poor diet may suggest a nutritional deficiency.
- Chronic infections, such as HIV and TB, renal failure, rheumatoid arthritis, or drugs used to treat these conditions may be associated with anaemia.

Examination

Clinical assessment has low sensitivity and specificity for mild–moderate anaemia. Signs include:

- Pallor of mucous membranes or nail beds (sensitivity 50–70% for moderate to severe anaemia).
- A compensatory hyperdynamic circulation (tachycardia, bounding pulse, cardiomegaly, systolic flow murmur).
- Severe, decompensated anaemia → shock (i.e. thirst, sweating, cold extremities, hypotension, and cardiac failure). These signs warrant fluid replacement or, where it can be performed safely, blood transfusion (➲ Blood transfusion, p. 467).

Laboratory diagnosis of anaemia

Measure the Hb or PCV (or HCT) of venous or capillary blood. For capillary samples from a finger or heel prick, the first few drops of blood should be wiped away to encourage free flow. Avoid squeezing—tissue fluid causes dilution (Box 10.1).

Box 10.1 Measuring Hb

Hb can be measured photometrically, but this requires laboratory equipment and skill.

The HemoCue Hb301 system is portable, battery-operated, and designed for accurate measurement of Hb in tropical conditions. It uses whole blood, and is simple and rapid.

The WHO Hb colour scale can be used where no power or equipment is available and an approximate Hb estimation is adequate. The colour of a drop of blood on chromatography paper is matched against a colour scale representing blood of Hb in 2g/dL increments (range 4–14g/dL). It is simple and cheap, but the correct filter paper must be used and it must be read under good light.

Measurement of PCV or HCT requires a microhaematocrit centrifuge and electricity but can be carried out by non-technical staff. Blood is taken into capillary tubes from a finger prick and centrifuged for 5min. This separates cells and plasma and the ratio of the length of RBC column to the total length of the blood sample = HCT (%). Where only HCT available, Hb (g/dL) may be crudely estimated as ~1/3 of the HCT (%). The accuracy of this estimation varies with age and Hb level, and is least accurate in children <5yrs.

Box 10.2 Classification of anaemia according to RBC size*

Microcytic (low MCV)

- Iron deficiency.
- Thalassaemia.
- Anaemia of inflammation.
- Lead poisoning.
- Sideroblastic anaemia.

Normocytic (normal MCV)

- Acute blood loss.
- Anaemia of inflammation.
- Marrow hypoplasia or infiltration.
- Chronic infection.
- Renal failure.

Macrocytic (high MCV)

- Folate deficiency.
- B_{12} deficiency.
- Drugs affecting DNA metabolism.
- Rare enzyme defects.
- Myelodysplasia.
- Alcohol.
- Liver dysfunction.
- Hypothyroidism.
- Haemolytic anaemia.
- Neonate (normal).

* Normal MCV = 76–96fL.

Iron-deficiency anaemia

This is one of the most common causes of anaemia worldwide.

Causes of iron (Fe) deficiency

- ↑ *Fe losses*: menstrual, GI infections (e.g. hookworm, whipworm, amoebiasis), peptic ulceration, carcinoma, oesophageal varices, haemoptysis, haematuria.
- ↑ *Fe requirements*: lactation, puberty, infancy (Box 10.3).
- ↓ *Intake*: ingestion of only milk (human or cow's) beyond 6mths of age; lack of red meat and/or legumes.
- ↓ *Fe absorption*: ingesting inhibitors of Fe absorption with meals (tea, milk, phytates present in grain); achlorhydria, malabsorption.

Clinical features

Brittle nails, koilonychia, angular stomatitis, glossitis, dysphagia (Plummer–Vinson syndrome = Fe-deficiency anaemia + oesophageal web).

Laboratory features

Low serum ferritin (<20 micrograms/L) is specific, but can be insensitive as it is an acute phase protein. Ferritin >100 micrograms/L generally excludes Fe deficiency, even in the setting of infection.

Management

- Ferrous sulfate 200mg tds for adults or 9mg/kg od for children from age 6yrs (1mg ferrous sulfate contains ~3mg elemental iron). Expect ↑ in Hb 1–3g/dL after 4wks of therapy if Fe deficiency is the cause of anaemia (this can be used as a diagnostic test). Continue Fe therapy for 3mths after normalization of Hb to replenish stores.
- Identify and treat the underlying cause and any other haematinic deficiencies (e.g. folate) (Box 10.4). NB: WHO guidance for therapy of severe anaemia is to treat empirically with Fe plus folic acid e.g. 200 micrograms <2yrs of age, 400 micrograms for children >2yrs and adults daily (https://www.who.int/nutrition/publications/micronutrients/guidelines_for_Iron_supplementation.pdf).
- Severe anaemia + signs of heart failure may require blood transfusion.

Notes

- Severely malnourished children should not receive Fe supplements until at least 15d into a feeding programme because of ↑ risk of bacterial sepsis and toxicity related to free radicals.
- To improve absorption, oral Fe preparations should be taken between meals and with vitamin C (e.g. orange juice, ascorbic acid tablets).
- Oral Fe should not be taken with antibiotics or antacids.

Side effects include GI upset (try lower dose or take with meals), constipation, green/black stools.

Box 10.3 Maternal and infant anaemia

Fe deficiency particularly affects children, and pregnant or breastfeeding women. Supplementary maternal Fe or Fe + folic acid can prevent anaemia and iron deficiency at term. If the mother has sufficient Fe stores, a neonate is born with enough stores to last 6mths. After 6mths, Fe requirements must be met from the diet; requirements ↑ with rate of growth. Useful guidance on reproductive health topics are available at: http://apps.who.int/rhl/pregnancy_childbirth/en/ and http://apps.who.int/rhl/newborn/en/.

Box 10.4 Prevention of iron deficiency

- *Nutritional advice*: eat meat and legumes with vitamin C (e.g. orange juice) and avoid tea, dairy products, or cereals as these ↓ Fe absorption.
- *Prophylactic Fe supplements*: WHO recommends these for women of child-bearing age and children >6mths where the prevalence of anaemia is >40%. However, these guidelines are controversial because of ↑ malaria and other infections when supplements given to children in malarial areas. Supervised weekly/twice weekly supplementation is effective for the prevention of Fe deficiency in school children.
- *Antihelminthics*: empiric treatment may be helpful in those with anaemia where helminth infections are common.

Anaemia of inflammation

This anaemia is associated with chronic inflammatory or malignant disease. There is ↓ RBC production, abnormalities of Fe utilization, and ↓ erythropoietin levels and/or response. These abnormalities are mediated by inflammatory cytokines and production of hepcidin, which blocks the release of Fe from enterocytes and macrophages.

Causes of chronic inflammatory disease

- *Infectious*: e.g. TB, HIV, lung abscess, osteomyelitis, pneumonia, SBE.
- *Non-infectious*: e.g. RA, SLE, other connective tissue disorders, sarcoidosis, Crohn's disease.
- *Malignancy*: e.g. carcinoma, lymphoma, sarcoma.

Differential diagnosis: anaemia of chronic renal failure, hypothyroidism, hypopituitarism, other microcytic anaemias (➲ Box 10.2, p. 450).

Clinical features Those of anaemia, plus those relating to underlying diagnosis.

Laboratory features Mild normocytic (occasionally microcytic), normochromic anaemia. Low reticulocyte count for degree of anaemia. ↓ serum Fe and TIBC. Normal or ↑ serum ferritin and a low/normal transferrin saturation. ↑ ESR, CRP.

Management

- *Treat underlying cause*: blood transfusions are a last resort. Fe overload may complicate repeated transfusions (➲ Blood transfusion, p. 450).
- Anaemia of inflammation may be complicated by another form of anaemia (e.g. Fe, vitamin B_{12}, or folate deficiency), renal failure, bone marrow failure, hypersplenism, or endocrine abnormality.
- Ferritin <100 micrograms/L may suggest concomitant Fe deficiency, but there is little response to oral Fe because of the block of Fe uptake in the small bowel. IV Fe may be required (Box 10.5).

Box 10.5 Intravenous iron

Worldwide, 50–60% of anaemia is caused by iron deficiency. Often, iron supplementation is given empirically. Failure to respond to oral Fe may be due to malabsorption, poor adherence, ongoing Fe loss, concomitant anaemia of chronic disease, iron-refractory iron deficiency, or an erroneous diagnosis. The first three may respond to IV iron thereby avoiding transfusion. The first dose should be given slowly because of the risk of adverse reactions (e.g. anaphylaxis, local irritation). IM iron injections are not recommended—they are painful, carry a risk of abscess formation, and absorption is unpredictable.

Macrocytic anaemias

Folate deficiency

Folic acid in green vegetables and fruits is absorbed in the duodenum and jejunum. Folate stores are limited and clinical deficiency occurs <2mths. States of rapid cell division (e.g. pregnancy, haemolytic anaemia) ↑ folate utilization and require prophylaxis. ↓ dietary intake (e.g. in alcoholics, the malnourished) can also → deficiency. Combined vitamin B_{12} and folate deficiency is common (Table 10.4).

Vitamin B_{12} deficiency

Vitamin B_{12} is present in meat or dairy products. Absorption of vitamin B_{12} requires proteases and binding factors released in the stomach, combined with intrinsic factor before uptake in the terminal ileum. Stores of vitamin B_{12} take 2–3yrs to deplete. Vitamin B_{12} is essential for DNA production. Folate acts as a co-factor, → similarity of their deficiency states. There are unique neurological manifestations of vitamin B_{12} deficiency.

Clinical features

Mild jaundice, glossitis, angular stomatitis, purpura (↓ platelets), sterility, skin pigmentation, and ↑ susceptibility to infections. Neuropathy, subacute combined degeneration of the cord (↓ vibration sense, hypertonia, weakness, and sensory ataxia, see ➲ Neurology, p. 434), psychosis, and dementia occur.

Laboratory findings

↑ MCV and MCH, normal MCHC, ↓ reticulocytes, ↓ WCC, ↓ platelets in severe cases.

Blood film

Oval macrocytes, hypersegmented neutrophils. Mildly ↑ unconjugated bilirubin and ↑ LDH. ↓ serum vitamin B_{12} and folate levels.

Management

Replacement therapy

- *Folic acid 5mg oral od for 4mths (children >1yr and adults)*: maintenance requirements depend on underlying disease. Consider coexisting vitamin B_{12} deficiency and replace empirically if necessary—if combined deficiency, replacing folate alone may → neurological complications.
- *Hydroxocobalamin (vitamin B_{12})*: six injections of 1mg IM over 1–2wks and maintenance with 1mg every 3mths. Oral vitamin B_{12} can be given if malabsorption is excluded. Anaemia should resolve over months.

Prophylaxis

Improve diet. Consider prophylactic treatment (e.g. folic acid 400 micrograms/d) in pregnancy, severe haemolytic anaemia, after partial gastrectomy and ileal resection.

Table 10.4 Causes of folate and vitamin B_{12} deficiencies

	Folate	Vitamin B_{12}
↓ intake	Seasonal shortage Boiling bottle feeds Prolonged storage of food Anorexia Famine Inappropriate weaning foods Prolonged cooking/reheating Feeding infants with goat's milk Alcoholism	Breastfeeding by vitamin B_{12}-deficient mothers Strict veganism Alcoholism
Malabsorption	Diarrhoea in infancy Acute enteric infections Giardiasis Systemic infections (TB, pneumococcus) Strongyloidiasis Coeliac disease Crohn's disease	Pernicious anaemia Gastrectomy Chronic giardiasis HIV Ileocaecal TB Strongyloidiasis Tropical sprue Crohn's disease Fish tapeworm
↑ physiological demands	Growth Pregnancy/lactation	
↑ pathological demands	Haemolysis Malignant disease	
Metabolic		Nitrous oxide Chronic cyanide Intoxication (cassava)

Haemolytic anaemias

In haemolysis, RBCs are broken down and their components metabolized in the reticuloendothelial system in hepatic and splenic sinusoids. Under certain circumstances (e.g. sickling crisis, severe oxidative damage), RBCs lyse within the circulation. RBCs normally remain in the circulation for ~120d, but lifespan ↓ in haemoglobinopathies, enzymopathies, membrane defects, deposition of antibody or complement, or mechanisms outside the RBC. Normal bone marrow can compensate up to 5× faster RBC turnover (compensated haemolysis); if haemolysis exceeds this or there are haematinic deficiencies or associated disease → anaemia.

Laboratory findings

- ↑ *RBC destruction*: unconjugated hyperbilirubinaemia, ↑ LDH, ↑ urinary urobilinogen, ↑ faecal urobilinogen.
- ↑ *RBC production*: polychromasia, reticulocytosis → ↑ MCV.
- *Intravascular haemolysis*: ↓/absent haptoglobins, ↓ haemopexin, ↑ haem/methaemoglobin, +ve Schumm's test (methaemalbumin), haemosiderinuria, haem/methaemoglobinuria.

Genetic abnormalities of RBCs are common in the tropics. Despite the disadvantage of haemolytic anaemia in homozygotes, the heterozygous state provides some protection against severe malaria. This is by altering the environment within the RBC or by conferring resistance to various stages in the parasite's lifecycle.

Red cell membranopathies

Conditions may provide some protection against malaria due to ↓ penetration of the RBC by merozoites.

Hereditary spherocytosis

Usually autosomal dominant; mainly in northern Europeans.

- *Clinical features variable*: +ve FHx, mild anaemia (8–12g/dL), intermittent jaundice, splenomegaly, cholelithiasis.
- *Laboratory findings*: blood film shows spherocytes, ↑ MCH, ↑ reticulocytes, ↑ lysis in osmotic tests, membrane protein analysis by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), −ve direct antiglobulin test.
- *Management*: folic acid 5mg/d. Splenectomy if severely affected (➲ Splenomegaly, p. 475).

Hereditary elliptocytosis

Autosomal dominant. Usually asymptomatic; haemolysis may be severe in homozygotes. May be episodes of jaundice and moderate splenomegaly following infections.

- *Laboratory findings*: elliptical RBCs, parental studies, membrane protein analysis by SDS-PAGE.
- *Management*: is not usually required; folic acid supplements and splenectomy may help if haemolysis significant.

Southeast Asian hereditary ovalocytosis

Autosomal dominant. Common in Malaysia, Indonesia, Philippines, Papua New Guinea, and Solomon Islands. Not associated with haemolytic anaemia (Box 10.6).

Box 10.6 Acquired haemolytic anaemia

- *Drug-induced immune haemolytic anaemia*: occurs when drugs bind to RBCs (e.g. high-dose penicillin), form new RBC antigens (e.g. quinidine), or provoke autoantibodies (methyldopa, mefenamic acid, levodopa). A careful drug history (incl. herbal preparations) is crucial.
- *Autoimmune haemolytic anaemia*: can be caused by cold (IgM) or warm (IgG) antibodies. May be 1° (idiopathic) or 2° to lymphoproliferative disorders, malignancy, autoimmune diseases, or infections. Direct anti-globulin (Coombs test) test is +ve because the patient's RBCs are antibody-coated.
- *Warm AHA*: presents as chronic or acute haemolytic anaemia with splenomegaly. Treat any underlying causes. Treat with steroids (e.g. prednisolone 1mg/kg daily) until Hb >10g/dL, then gradually ↓. Consider splenectomy if steroids fail; blood transfusion in severe cases.
- *Cold AHA*: presents as chronic anaemia made worse by cold; associated with Raynaud's phenomenon and acrocyanosis. Treat underlying cause; steroids not helpful. Advise patient to keep warm. Chlorambucil can be helpful if underlying lymphoma. Splenectomy does not usually help as IgM-coated cells are removed in the liver.
- *Paroxysmal cold haemoglobinuria*: may follow mumps, measles, chickenpox, syphilis, esp. in children.

Glucose-6-phosphate dehydrogenase deficiency

G6PD deficiency → oxidative damage of the RBC and haemolysis. Fig. 10.1 shows the global distribution of G6PD deficiency, which affects 400 million people. Superimposed are three zones where different G6PD variants occur: zone I (GdMediterranean), zone II (GdMediterranean, GdCanton, GdUnion, GdMahidol), and zone III (GdA). GdA → moderate, intermittent haemolysis, whereas GdMediterranean and GdCanton are more severe. G6PD deficiency is X-linked, so is commoner in males.

Clinical features Mostly asymptomatic, but episodic haemolysis can be severe, esp. in non-African mutations. Chronic haemolysis is unusual. In Africa, adults with G6PD deficiency usually only suffer mild haemolysis but neonates may develop severe hyperbilirubinaemia and kernicterus. Haemolytic episodes are precipitated by infection and drugs.

Diagnosis

- *Between attacks*: ↓ G6PD enzyme activity in hemizygous males and heterozygous women.
- *During a crisis*: blood film may show 'bite' and 'blister' cells. Testing during a crisis often unhelpful because haemolysis eliminates older RBCs, which have lowest G6PD activity, so only youngest RBCs (which may have normal G6PD activity) remain. Following crisis, delay testing for 6wks. In more severe variants, a greater proportion of RBCs have low G6PD.

Management

- Treat underlying infection.
- Avoid drugs that precipitate haemolysis (Box 10.7).

Maintain a high urine output

- Give folic acid supplements if recurrent haemolysis.
- G6PD-deficient babies are prone to neonatal jaundice: may need phototherapy and exchange transfusion.

Box 10.7 Examples of drugs to be avoided in G6PD deficiency

- *Antimalarials*: primaquine, sulfadoxine-pyrimethamine, pyrimethamine-dapsone.
- *Sulfonamides/sulphones*: co-trimoxazole, sulfanilamide, dapsone, sulfasalazine, sulfamethoxazole.
- *Antibiotics*: nitrofurans, nalidixic acid.
- *Analgesics*: phenacetin.
- *Antihelminths*: naphthol, stibophen, nitrodazole.
- *Miscellaneous*: naphthalene, fava beans, methylene blue, trinitrotoluene, amylnitrates, phenylhydrazine.

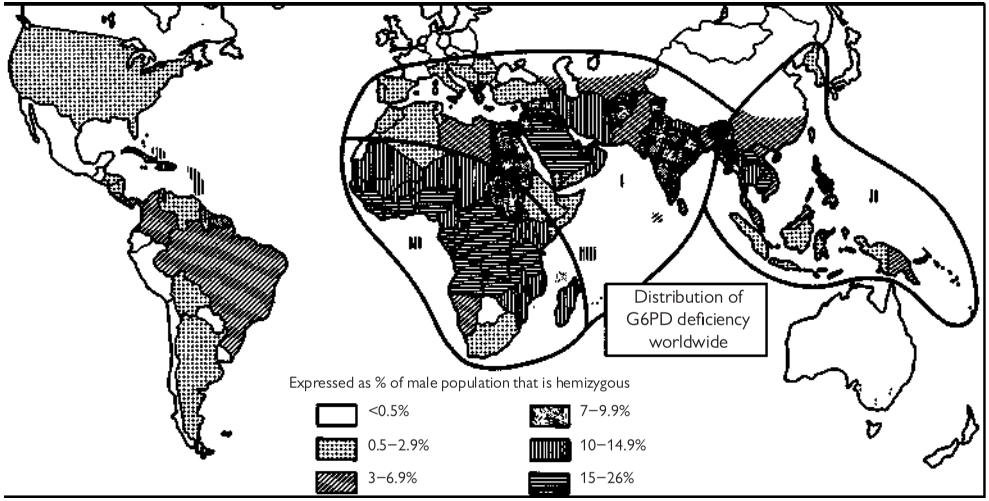

Fig. 10.1 Global distribution of G6PD deficiency.

Sickle cell anaemia

The sickle gene is common in equatorial Africa (up to 25%), Saudi Arabia, and southern Asia, but less common in the Mediterranean and the mixed populations of the Americas (~5%) (Fig. 10.2). Due to a single point mutation in the Hb β-globin gene chain. When deoxygenated, HbS molecules polymerize into elongated structures → RBCs deform and haemolyse. Sickled RBCs are rigid and block the microcirculation in various organs → infarcts (Fig. 10.3).

The heterozygous state (sickle trait; HbAS) is usually asymptomatic; it → protection against malaria. Sickle cell disease occurs if homozygous (HbSS) or co-inheritance of another β-globin chain disorder (e.g. HbC). Sickle cell disease and G6PD deficiency may coexist in some regions.

Other sickling syndromes

- *HbSC disease* occurs in west Africa. There is less haemolysis than with HbSS. May present only in adulthood. Splenomegaly is common. Anaemia is less severe than in HbSS but vaso-occlusive complications (e.g. avascular necrosis, proliferative retinopathy) are prominent and may → significant disability in adulthood. Electrophoresis shows two haemoglobin bands, HbS and HbC. The blood film has many target cells and irregularly contracted cells.
- *HbSB^0 thalassaemia*: occurs mostly in North Africa, Sicily, and mixed populations of the Americas. Clinically similar to HbSS, there is a lower incidence of stroke. The blood film shows hypochromic microcytic RBCs and target cells. Hb electrophoresis shows HbS, absence of HbA, and ↑ HbA_2 and HbF. Diagnosis by parental studies or DNA analysis.
- *HbSB$^+$ thalassaemia*: most commonly seen in West Africa. Clinically milder than HbSS. Proliferative retinopathy occurs. Hb electrophoresis shows HbA 5–30%, HbS 70–95%.
- *HbSD^{Punjab} and HbSO^{Arab}*: as severe as HbSS. HbD occurs in Sikh and mixed populations.
- *HbSE, HbS^{Lepore}, and HbS/HPFH*: (hereditary persistence of fetal haemoglobin). All these are milder than HbSS.

Clinical features of sickle cell anaemia

Severe haemolytic anaemia punctuated by severe pain crises. Young patients have alternate periods of good health with acute crises. Later, chronic ill health supervenes due to organ damage. Symptoms begin after 6mths of age as the HbF level ↓. The first signs are often of acute dactylitis due to occlusive necrosis of the small bones of the hands and feet, → digits of varying length. The long bones are affected in older children and adults. Anaemia (Hb 6–8g/dL; reticulocytes 10–20%, see laboratory findings in Box 10.8) is well tolerated because of cardiac compensation and a lower affinity of HbS for O_2.

Complications depend on other factors incl. the proportion of HbF and the ratio of α- to β-globin chains, which may be modified by concomitant α thalassaemia trait or conditions affecting β-globin chain production. For sickle cell disease in pregnancy, see Box 10.9, and in surgery, Box 10.10.

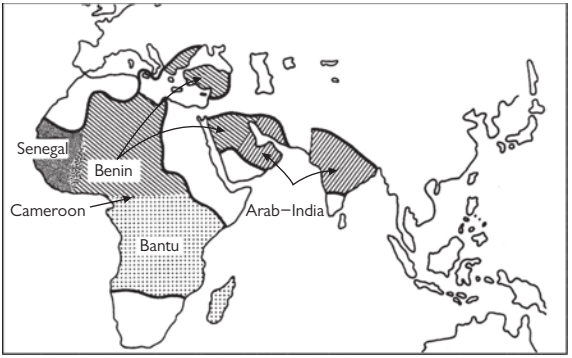

Fig. 10.2 Distribution of HbS gene and its various haplotypes (Arab-India, Bantu, Benin, Cameroon, Senegal) in the Mediterranean and West Asia.

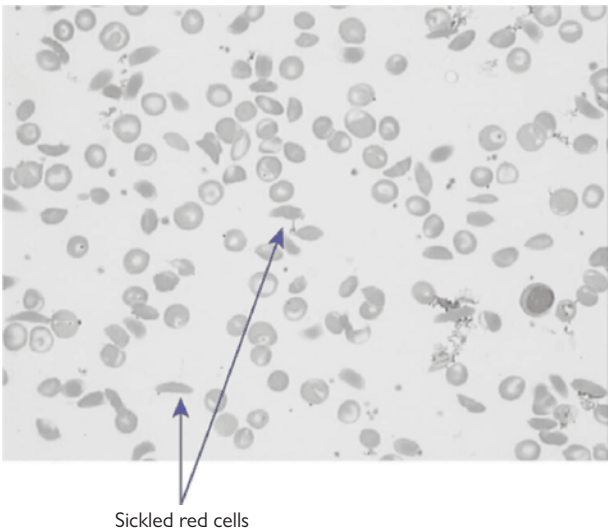

Fig. 10.3 Characteristic sickle-shaped RBCs in peripheral blood film in patient with homozygous sickle cell anaemia. Reproduced with permission from Provan, Drew, Baglin, Trevor, Dokal, Inderjeet, de Vos, Johannes, Kaya, Banu, and Theodoulou, Angela, 'Red Cell Disorders', in Drew Provan, Trevor Baglin, Inderjeet Dokal, and Johannes de Vos, *Oxford Handbook of Clinical Haematology* (4th edn, Oxford, 2015), Figure 2.7, © 2015, Oxford University Press.

Types of crises

- *Painful vascular-occlusive*: frequent, precipitated by infections, acidosis, dehydration, or hypoxia. Infarcts often occur in the axial skeleton, lungs, and spleen. Repeated splenic infarction → hyposplenism in adulthood. Crises can involve the CNS (in 7% of patients) and spinal cord.
- *Visceral sequestration*: due to sickling within organs and pooling of blood. Requires emergency transfusion.
- *Chest*: pulmonary infiltrates on CXR, fever, chest pain, tachypnoea, cough, wheeze. There is often concomitant infection, microvascular occlusion, and bronchoconstriction. Chest crises can arise during a painful crisis; patients should be monitored carefully for this complication, which can be fatal.
- *Haemolytic*: ↑ haemolysis → ↓ Hb. Usually accompanying a painful crisis. Concomitant G6PD deficiency may ↑ haemolysis.
- *Aplastic*: arrested RBC production due to parvovirus infection and/or folate deficiency. Characterized by a sudden ↓ in Hb and reticulocytes; emergency blood transfusion can be life-saving.

Complications of sickle cell anaemia

Pulmonary fibrosis, pulmonary hypertension, stroke, proliferative retinopathy, cardiomegaly, renal concentrating defect, papillary necrosis, osteomyelitis (often due to *Salmonella* spp.), skin ulcers, proliferative retinopathy, priapism, hepatic dysfunction, pigment gallstones. Infectious complications are the most common cause of death. Hyposplenism → risk of sepsis with encapsulated bacteria (e.g. pneumococcus, meningococcus, *Haemophilus*). Survival is linked to socioeconomic conditions.

Box 10.8 Laboratory findings

- Hb 6–8g/dL, ↑ reticulocytes, normal MCV (if MCV low, consider Fe deficiency or thalassaemia).
- Sickle cells and target cells in the blood film; +/− features of splenic atrophy (e.g. Howell–Jolly bodies).
- *Screening tests*: sickle solubility test (dithionate and Na_2HPO_4) will be positive if >20% HbS. Also positive in sickle cell trait and compound heterozygotes. False –ve results occur in infants <6mths because of HbF.
- *Detection of HbS or other Hb variants*: Hb electrophoresis, iso-electric focusing, and HPLC. Can provide quantification of abnormal Hb, but available only at referral centres. Expect 30–40% HbS with HbAS (35% with concomitant α thalassaemia), >80% with HbSS.

Management

Support to maintain health in sickle cell disease (Box 10.11).

Painful sickling crises

- Exclude other causes of pain.
- *Keep hydrated*: oral, NG, or IV (if other routes have failed).
- Keep patient warm.
- O_2 therapy is only necessary if hypoxic.

Box 10.9 Sickle cell disease and pregnancy

Sickle cell disease → intrauterine growth retardation, pre-eclampsia, pre-term labour, *in utero* fetal death, and ↑ risk of sickle-related complications in the mother. Sickle cell trait is not a problem, but UTIs more common.

- Early access to antenatal care is important to allow monitoring for complications.
- Folic acid supplements essential: prevent megaloblastic anaemia and birth defects.
- Delivery should be non-operative where possible. Consider preoperative exchange transfusion before Caesarean section in complicated pregnancies.
- Test neonate for Hb variants, confirm at 3–6mths.

Box 10.10 Sickle cell disease and surgery

Significant complications in 20–60%, depending on the procedure. Improved outcomes with either top-up or exchange transfusions. Chest physiotherapy useful. Minor operations can be carried out safely without preoperative transfusion, providing patients are well hydrated.

- *Effective pain relief*: can ↓ time spent in hospital; undertreating can → drug-seeking behaviour and a pain-orientated personality.
- Parenteral opiates are often required, but IM route can → abscesses. Monitor response to analgesia; use a pictorial pain scale in children.
- *Oral analgesia*: NSAIDs helpful for bone pain. Give with ulcer-protection (e.g. H_2-receptor antagonist or PPI) and monitor renal function. Oral opioids are effective.
- *Inhaled nitric oxide*: risk of subacute combined degeneration of cord with repeated/prolonged use.

Infections

- Infections are common causes of death in sickle cell anaemia.
- *Treat bacteraemia rapidly*: start antibiotics empirically if febrile and acutely unwell. Cover *Streptococcus pneumoniae*, Hib, *Neisseria meningitidis* (e.g. ceftriaxone 2g od). Where microbiological diagnosis is possible, send urine and blood for culture, do LP if features of meningitis, CXR for suspected pneumonia/chest syndrome.
- *Proven/suspected meningitis*: treat with ceftriaxone for 2wks.
- *Acute chest syndrome*: usually triggered by infection. Cover *S. pneumoniae*, Hib, *Mycoplasma*, and *Chlamydia pneumoniae* (e.g. ceftriaxone and erythromycin). Supportive measures, incl. bronchodilators. Consider exchange transfusion if severe (Box 10.12). Incentive spirometry (use of spirometer to guide deep respirations at regular intervals) can ↓ risk of acute chest syndrome developing from painful crisis involving ribs or back.
- *Osteomyelitis*: confirm organism with cultures, or empirically cover *Salmonella paratyphi*, *Escherichia coli*, and *Staphylococcus aureus* (e.g. ceftriaxone and ciprofloxacin). Requires at least 6wks of therapy; may require surgery. Monitor closely for recurrence (➲ Soft tissue infections p. 587).

- *Malaria*: non-specific cause of fever and associated with mortality in sickle cell anaemia.
- *Good supportive care*: is essential to prevent other complications. Monitor fluid balance carefully to prevent overload; treat pain and hypoxia.

Box 10.11 Maintenance of health in sickle cell disease

- *Screening*: greatest mortality is among children <5yrs so early diagnosis is important. Universal screening in some countries.
- *Education*: general health education. Seek medical attention early (esp. if high fever), to use clean drinking water and insecticide-treated bed nets.
- Genetic counselling to identify affected relatives/partners and to plan pregnancy.
- *Avoid factors precipitating crisis*: esp. dehydration, hypoxia, infections, cold.
- Folic acid supplements: 1–5mg/d.
- *Protect against infection*: vaccinate against *S. pneumoniae*, Hib, meningococcus, hepatitis B, influenza. Educate parents/patients about ↓ mortality with prophylactic penicillin (125mg oral bd for children <5yrs, 250mg bd thereafter).
- Advise lifelong antimalarial prophylaxis in endemic areas.
- *Detection of acute splenic sequestration*: teach parents to palpate the spleen and to attend clinic if the child becomes unwell, with an enlarging spleen.
- *Screen for long-term complications*: e.g. annual fundoscopy (for retinopathy) from 15yrs.
- *Hydroxycarbamide*: ↓ frequency of crises, chest syndrome, hospitalizations, and mortality; should be considered for those with painful crises >2–3× per year. Avoid around conception and pregnancy.

Box 10.12 Indications for transfusion in sickle cell disease

↑ Hb levels above steady state ↑ thrombotic risk. Indications for transfusion include correction of blood loss or ↓ production or sequestration (e.g. postoperatively; during sequestration or aplastic crises; during acute severe illness).

Exchange transfusions: sometimes performed to ↓ HbS%, and thus ↓ risk of vaso-occlusion. Aim for Hb 10g/dL, HCT 32%, HbS <30%. Exchange transfusions are beneficial (e.g. to prevent/↓ risk of stroke, during pregnancy in women with a past history of severe complications).

Thalassaemia

α Thalassaemia

α Thalassaemia is a defect or deletion of at least one of four α-globin genes. α^+ thalassaemia trait is common in Africans and does not cause anaemia. α^0 thalassaemia trait is more common in Asia and Mediterranean region → mild anaemia, ↓ MCV, ↓ MCH; hypochromic, microcytic RBCs and target cells. More severe forms of α thalassaemia affect the fetus and neonate because fetal Hb (α2γ2) requires α-globin chains. α thalassaemia is characterized by haemolysis rather than ineffective erythropoiesis.

HbH disease

β-globin chains (HbH) that form inclusions in RBCs; can be detected with specific stains or Hb electrophoresis. HbH very poor at O_2 delivery. HbH levels are 5–30% with Hb 7–10g/dL. Children may have growth retardation and skeletal abnormalities, +/– hepatosplenomegaly. Transfusions are not usually required. Splenectomy may be of benefit.

Hb Bart's hydrops fetalis The fetus lacks all α genes and is stillborn or dies shortly after delivery.

β Thalassaemia

Caused by mutations of the β-globin genes among people originating from southern Europe, Africa, Middle East, India, and Southeast Asia. Excess free α-globin chains precipitate as inclusion bodies in RBC precursors, → RBC destruction → ineffective erythropoiesis and ↑ splenic uptake of RBCs. There is compensatory ↑ Fe uptake and expansion of erythropoiesis incl. extramedullary sites. This expansion, together with Fe overload and hypersplenism, → clinical manifestations.

β Thalassaemia minor

Palpable splenomegaly and moderate anaemia during pregnancy. Can → compensatory placental hypertrophy and mild intrauterine growth retardation, but does not ↑ perinatal mortality.

Laboratory findings Mild anaemia (e.g. Hb 9–11g/dL); blood film shows moderate anisocytosis, microcytosis (MCV <76fL, MCH <26pg), hypochromia with a few target and tear drop cells. Basophilic stippling may occur. Hb electrophoresis shows ↑ HbA_2 (>3.5%); HbF may also be ↑. *Note*: Fe deficiency can mask β thalassaemia minor. Test for thalassaemia when patient is Fe replete.

Management Diagnosis avoids future treatment of hypochromic anaemia with Fe, education, and genetic counselling.

β Thalassaemia intermedia

Causes mild to severe anaemia. Generally, splenomegaly, bony expansion, and complications of Fe overload are present.

Laboratory findings Features intermediate between β thalassaemia major and minor.

General management
Screen family; active immunization, clean water, use impregnated bed nets, early attendance at medical facilities if unwell or febrile. Specific measures incl.: folate 5mg/day for adults; transfusion if severe anaemia or failure to thrive, or to ↓ erythroid expansion (e.g. if skeletal deformity); iron chelation if ferritin >1000 micrograms/L even if not regularly transfused; splenectomy if hypersplenism.

β Thalassaemia major

- Untreated, most patients die <5yrs from cardiac failure or infection.
- Failure to thrive at 3–6mths, when the switch from γ- to β-chain production should take place; puberty often delayed.
- Hepatosplenomegaly due to haemolysis, extramedullary haemopoiesis, and later Fe overload from transfusions. Splenomegaly ↑ blood requirements by ↑ RBC destruction and pooling.
- Bone expansion as a result of intense marrow hyperplasia; → skeletal deformity, incl. prominent frontal and parietal bones, maxillary enlargement, and flattening of the nasal bridge. There is osteoporosis (↑ fractures) and skull bossing with 'hair-on-end' appearance on X-ray.
- Infections ↑: defective splenic function, Fe overload. Severe gastroenteritis caused by *Yersinia enterocolitica* is associated with desferrioxamine treatment. Transmission of viral hepatitis is also ↑, probably due to Fe overload and transfusions.
- Fe overload due to transfusion therapy (each 500mL unit of blood contains 250mg of Fe) and ↑ Fe absorption. Fe accumulation → liver damage, failure of growth, delayed or absent puberty, diabetes, hypothyroidism, hypoparathyroidism, and myocardial damage. In the absence of intensive iron chelation, death occurs in the 2nd or 3rd decade, usually from CCF or cardiac arrhythmias. Clinical signs usually appear after >50U (12g of Fe), but organ damage and skin pigmentation occur before this.

Laboratory findings Severe hypochromic microcytic anaemia with ↑ reticulocyte count. Blood film shows many nucleated RBCs, tear drop and target cells, as well as cells of variable morphology and basophilic stippling. Electrophoresis shows absent HbA; ↑ HbF, ↑ HbA_2.

Management Refer to specialist centre. Treat as for thalassaemia intermedia, plus commence Fe chelation (e.g. desferrioxamine by SC infusion) when ferritin >1000 micrograms/L, or signs of organ damage.

Start regular transfusions around 6–12mths old when growth chart shows failure to thrive. These help suppress patient's ineffective erythropoiesis, prevent bony deformity, and normalize growth. Maintain Hb >9.5g/dL.

- Give HBV vaccination.
- Supplement folic acid.
- Splenectomy if hypersplenism.
- Monitor for complications, e.g. gallstones, CCF, pulmonary hypertension, aplastic crises.

Blood transfusion

Blood transfusion can be life-saving but transfusion-associated risks are high. In countries where supplies of safe blood are scarce, the following may guide the decision to transfuse:

- Anaemic heart failure.
- Hb <5g/dL with symptoms.
- Hb <4g/dL in any situation.
- Acute blood loss → shock or signs of heart failure despite IV fluids.
- Need for emergency major surgery with preoperative Hb <7g/dL.

Whole blood is used for most transfusions in resource-poor countries.

Ensuring blood safety and supply

Measures to make safe blood available:

- Prevention of unnecessary transfusions.
- Donor screening with a questionnaire to exclude those at high risk of transfusion-transmissible infections (e.g. HIV, hepatitis C).
- A panel of voluntary, unpaid donors who have repeatedly tested –ve for transfusion-transmissible infections and who pass a basic medical test (check pulse, BP, screen for anaemia and other major illnesses).
- Standardize procedures for collection, storage, testing, and administration of blood incl. adequate controls and quality assurance (e.g. two grouping techniques should be used in parallel to prevent fatal ABO-incompatible transfusion reactions).
- Screening all blood for transfusion-transmissible infections, including HIV, hepatitis B, syphilis, hepatitis C, and, if appropriate, trypanosomiasis and malaria.
- Regular training for those involved in transfusion to ensure competency and safety.
- Use of a closed system allowing collection into blood bags with anticoagulant, testing and, if necessary, division, or fractionation of products.
- Appropriate storage in thermostatically controlled fridges with back-up power supplies.
- A labelling system for blood bags, samples, and patient identification as well as a procedure of checks at the bedside to ensure the correct unit is administered to the correct patient.

Administration of blood

Blood should only be removed from the fridge immediately prior to use. When administering a blood transfusion:

- Check the patient details with those of unit of blood to ensure it has been issued to that patient and is compatible with blood group of the patient.
- Give IV via a blood-giving set with a filter.
- Keep a record of the volume and units given.
- Observe the patient for the first 10min of a transfusion. Check pulse, BP, RR, temperature at start of transfusion and after 15–30min, and every hour during the transfusion.
- Monitor for signs of fluid overload.

Exchange transfusions

In certain situations, an exchange transfusion is indicated to ↓ the risk of volume overload or to ↓ the concentration of patients' RBCs or plasma, e.g. in:

- Heart failure 2° to anaemia.
- Complications of sickle cell disease.
- Haemolytic disease of the newborn.
- Hyperbilirubinaemia in neonates.

Specialist advice should be sought regarding details of volumes and procedures for exchange transfusion.

Transfusion reactions

Severe transfusion reaction

- May be due to ABO incompatibility or bacterial contamination of the unit. Heralded by pain at site of cannula, back/chest pain, agitation, dyspnoea, nausea, flushing, or hypotension.
- Stop the transfusion immediately. Do not flush giving set.
- IV access, catheterize patient, and start fluids to ensure diuresis.
- Monitor renal and liver function, clotting parameters, haemoglobinuria.
- Give broad-spectrum antibiotic, e.g. ceftriaxone, if possible after taking blood cultures and send donor blood unit for culture.
- Give bronchodilators if wheezing; give antihistamine and IV hydrocortisone as for allergic reaction.
- Laboratory to re-crossmatch unit, repeat patient's grouping, and monitor for development of RBC antibodies.

Simple febrile and allergic reactions

If temperature ↑ by >1°C from baseline or the patient develops urticarial rash or itching, stop the transfusion, check vital signs, give paracetamol, and, if the patient remains well after 15min, restart the transfusion at a slower rate.

Delayed transfusion reaction

Usually occurs 5–10d post transfusion and is due to sensitization to RBCs following previous transfusions or pregnancy.

Clinical features Fever, jaundice, and anaemia.

Laboratory features Samples should be taken for grouping, direct Coombs' test, repeat cross-matching, and antibody screening and results compared with a pre-transfusion sample.

Effects of HIV/AIDS

Anaemia

Common in individuals with advanced HIV, usually multifactorial, and carries poor prognosis. Anaemia of chronic disorders related to OIs and TB is common; HIV itself ↓ erythropoiesis. Anaemia associated with chronic disorders may be far more severe than that seen in HIV–ve individuals. Bone marrow infiltration by MAC, TB, or other OIs may also contribute (often accompanied by other cytopenias). Malnutrition and malabsorption may → vitamin B_{12}, folate, and iron deficiency. Avoid inappropriate overprescription of iron supplementation for HIV-related anaemia, as iron tablets → GI side effects, which may ↓ tolerance of other medication.

Other causes of anaemia in HIV

Medication

AZT (causes anaemia with or without neutropenia), 3TC (pure red cell aplasia, rare), co-trimoxazole (esp. at higher doses), amphotericin and rifabutin (marrow suppression), dapsone and primaquine (haemolysis in G6PD deficiency). Drug-induced haemolytic anaemia may also occur.

Infections

Parvovirus B19 can → chronic erythroid hypoplasia in HIV. In endemic areas, malaria should always be considered.

Malignancies and premalignant conditions

Lymphoma or Castleman's disease may → bone marrow infiltration or haemolytic anaemia. GI KS may → GI blood loss.

Immune mediated

Coombs +ve autoimmune haemolytic anaemia, cryoglobulinaemias, and TTP may all → anaemia.

Thrombocytopenia

The commonest cause is HIV-related idiopathic thrombocytopenic purpura (ITP). Other causes incl. drugs (e.g. co-trimoxazole), marrow infiltration (OI, TB, or lymphoma), nutritional (vitamin B_{12} or folate), malaria, and hypersplenism.

Management

Stop/substitute culprit drugs. Bone marrow biopsy if bicytopenia or pancytopenia or if systemic symptoms suggesting OI or lymphoma. ITP is treated with corticosteroids (prednisolone 1mg/kg) and ART initially. HIV-related ITP is an indication for ART.

Neutropenia

May occur related to HIV itself, marrow infiltration (e.g. TB), or drugs (e.g. co-trimoxazole, AZT). Also vitamin B_{12} and folate deficiency.

Coagulopathy

HIV+ve individuals have ↑ risk of DVT and pulmonary embolus. This may be related to acquired protein C and S and antithrombin III deficiency and perhaps antiphospholipid antibodies. Thrombosis ↑ during active TB, presumably because of systemic inflammation and immobility.

Acute leukaemias

An excessive proliferation of immature haematopoietic cells → blasts in the peripheral blood. Without treatment, patients with acute leukaemias have a median survival of months. Chemotherapy may be curative. This is not the case with indolent haematological malignancies, which may not require treatment at diagnosis but are incurable with standard chemotherapy.

Diagnosis

Diagnosis of acute leukaemias relies on analysis of blood and bone marrow samples to establish origin of malignant cells and associated genetic abnormalities.

Treatment

Treatment is with cycles of chemotherapy, and requires urgent transfer to a specialist centre. Normal haematopoietic tissue is also affected by chemotherapy, → anaemia, neutropenia, and thrombocytopenia. Tumour lysis syndrome may occur with first cycle and is an emergency (Box 10.13). Supportive care is essential: RBC and platelet transfusions may be required and there is a significant risk of neutropenic sepsis.

Acute lymphoblastic leukaemia (ALL)

ALL has peaks at 2–5yrs and >40yrs. Poor prognostic markers include age <1 or >10yrs and >30yrs; presenting WBC >50 × 10^9/L, and certain cytogenetic abnormalities. Clinical features include bone pain, lymphadenopathy, hepatosplenomegaly, anaemia, haemorrhage, and infections.

Acute myeloblastic leukaemia (AML)

AML has a median age at diagnosis of 70yrs. Clinical features are similar to ALL except that in Africa 10–30% of patients may present with a solid tumour (chloroma), e.g. in the orbit or skin. Gum hypertrophy and DIC can be features. Risk factors incl. exposure to benzene, radiation, and previous cytotoxic therapy. Poor prognosis is associated with age >55yrs, poor general state of health, and specific cytogenetic abnormalities. Where specialist care is not available, hydroxycarbamide (adult dose 1–2g/d) may temporarily ↓ WBC and symptoms.

For causes of changes in WBC counts, see Box 10.14.

Box 10.13 Tumour lysis syndrome

AKI characterized by ↑ uric acid, ↑ K^+, ↑ LDH, ↑ PO_4, ↑ creatinine, ↓ Ca^{2+}. Caused by release of toxic components upon cell death in leukaemia and aggressive NHL. It can occur spontaneously, due to rapid tumour growth or more predictably, upon starting treatment. Occurs more commonly in the elderly, pre-existing renal impairment. Anticipate and prevent: allopurinol 100–200mg tds (adults), 100mg/m^2 tds (children, max. 400mg/d) aggressive IV hydration to ↑ urine output.

Box 10.14 Causes of changes in WBC counts

↑ WBC count

Neutrophilia >7.5 × 10⁹/L

- Physiological, e.g. pregnancy.
- Acute bacterial infections, e.g. pneumonia, UTI, abscess (incl. amoebic liver abscess).
- Tissue damage, inflammation, stress, e.g. burns, pancreatitis, diabetic ketoacidosis.
- Malignant disease.
- Drugs, e.g. steroids.

Basophilia >0.1 × 10⁹/L

- Myeloproliferative disorders.
- Allergic reactions.

Lymphocytosis >3.5 × 10⁹/L

- Childhood response to infections.
- Certain bacterial infections in adults, e.g. Brucellosis, pertussis.
- Viral and protozoal infections, e.g. CMV, EBV, toxoplasmosis.
- Lymphoproliferative disorders.

Monocytosis >1.0 × 10⁹/L

- Rarely, chronic bacterial infection, e.g. TB.
- Chronic myelomonocytic leukaemia.

Eosinophilia >0.5 × 10⁹/L

- Helminth infections, esp. acutely: e.g. hookworm, strongyloidiasis, schistosomiasis—values >3 × 10^9/L are likely to be due to Katayama fever, strongyloidiasis.
- Allergic/skin conditions, e.g. asthma, atopy, drugs, vasculitis, psoriasis; reactive to leukaemia/lymphoma, connective tissue disease.
- Convalescence from viral or other infections, especially in infants.

↓ WBC count

Neutropenia <1.5 × 10⁹/L, depending on local normal range

NB: some populations from Africa and the Middle East have a lower normal range of neutrophils, but rarely have prolonged severe neutropenia (<0.5× 10^9/L) and no ↑ risk of infection.

- Acute infection, e.g. dengue, overwhelming sepsis.
- Some chronic infections, e.g. visceral leishmaniasis, miliary TB, AIDS.
- Bone marrow failure or drugs, e.g. chloramphenicol.
- Peripheral consumption, e.g. hypersplenism, Felty's syndrome.
- Miscellaneous, e.g. ethnic, familial, cyclic, chronic, idiopathic.

Lymphopenia <1.5 × 10⁹/L

- Very common in many acute infections, e.g. TB, hepatitis, pneumonia.
- Drugs, e.g. corticosteroids.

Lymphoproliferative disorders

Non-Hodgkin's lymphoma (NHL)

A heterogeneous group of B- and T-cell tumours. Low-grade lymphomas are incurable and initially run an indolent course even without treatment. High-grade lymphomas are more aggressive but cure is achievable. High-grade NHLs are more common in Asia and Africa and, in Africa, are associated with malaria. Features include: lymphadenopathy, hepatosplenomegaly, ↓ weight, night sweats, pruritus, fever, pancytopenia. Most of these disorders will temporarily respond to corticosteroids if specialist treatment is not available, but beware tumour lysis in bulky high-grade disease.

Burkitt's lymphoma (BL)

Highly aggressive NHL, tumour may double time in 24–48h, rapidly fatal without treatment. Three clinical variants: endemic (related to EBV infection and common in malarial areas); sporadic; related to immunodeficiency (including HIV). It is the most common childhood cancer in tropical Africa. Commoner in boys, peak incidence 4–7yrs. Endemic form frequently involves the jaw, periorbital area but can involve any extranodal site. Sporadic BL presents most commonly with abdominal involvement (e.g. ileo-caecal intussusception). Steroids or a single dose of IV cyclophosphamide may provide temporary control but intensive chemotherapy is needed to achieve a 70–90% cure rate. Measures to prevent/treat tumour lysis should be taken (➲ Box 10.13, p. 470).

Hodgkin's lymphoma (HL)

More common in men, peaking in young adulthood and middle age. There are geographical variations in subtypes; nodular sclerosing HL predominates in published studies, but in developing countries, the mixed cellularity subtype is more common and linked to EBV exposure. HL usually presents as painless lymphadenopathy and 70–80% of cases are curable with standard radio/chemotherapy.

Chronic lymphocytic leukaemia (CLL)

Characterized by proliferation of mature, dysfunctional lymphocytes → infections or autoimmune haemolytic anaemia. More common in men, median age 60yrs. In temperate regions, the most common form of leukaemia. CLL may present with incidental lymphocytosis (5 to >100 × 10^9/L), lymphadenopathy, hepatosplenomegaly, infections, or bone marrow failure. Treatment consists of chemotherapy (e.g. chlorambucil) or if not available, steroids. Transfusions and antibiotics may be required.

Multiple myeloma (MM)

Plasma cell malignancy infiltrating bone marrow. Incidence ↑ in the islands of Pacific, Caribbean, and Africa compared to wealthy countries. Clinical features include bone pain, pathological fractures, osteopenia, ↑ Ca^{2+} (➲ Cancer, p. 682), renal failure, and bone marrow failure with anaemia, infection, and bleeding. Definitive treatment → median survival 3–5yrs, but where not available, steroids can be used. Supportive treatment incl. analgesia, transfusions, and bisphosphonates.

HTLV-1-associated adult T-cell leukaemia/lymphoma (ATL)

HTLV-1 is a retrovirus endemic in parts of the Caribbean, South America, central and southern Africa, and southern Japan. It causes ATL with a lifetime risk of 4% in those infected at a young age. HTLV-1 is also associated with chronic neurological conditions.

Transmission

Mainly by sexual contact and breastfeeding in endemic areas. Has also been transmitted by blood transfusion. In Europe and North America it is transmitted through IV drug use.

Clinical features

- *Acute ATL in 2/3 of cases*: high circulating lymphocyte count, lymphadenopathy, hepatosplenomegaly, hypercalcaemia, CNS involvement, skin lesions.
- *Lymphoma type*: clinically like NHL, but with poor prognosis.
- *Chronic ATL*: skin lesions, mild lymphocytosis, protracted course.
- *Smouldering ATL*: low peripheral lymphocyte count, skin lesions, remains stable for many years.

Diagnosis

FBC, WBC (lymphocyte count 30–130 × 10^9/L); blood film shows atypical lymphocytes with convoluted nuclei. HTLV-1 serology is +ve. Elevated serum Ca^{2+} common. CXR may show pulmonary infiltration, osteolytic lesions. Lymph node biopsy or bone marrow biopsy usually diagnostic.

Management

Combination chemotherapy for acute or progressive disease.

Myeloproliferative disorders

A group of disorders characterized by proliferation of haemopoietic stem cells. These cells retain their ability to differentiate, resulting in an excess of mature cells of predominantly one lineage. The disorders share systemic symptoms such as malaise, night sweats, fever, and ↓ weight. Often have splenomegaly; gout and pruritus may occur. These disorders are not curable, but may have a long survival if treated. Transformation to acute leukaemia or to marrow fibrosis occurs in a minority.

Polycythaemia

1° polycythaemia (polycythaemia rubra vera) is characterized by HCT >56% in females, >60% in males, ↑ neutrophils, and/or ↑ platelets, gout, splenomegaly, and, less commonly, thrombosis. 2° causes should be excluded.

Treatment

- Venesection to ↓ HCT to <45%.
- Aspirin (75mg od).
- Hydroxycarbamide for concomitant thrombocytosis or those whose HCT is not controlled by venesection.
- Median survival is >15yrs in younger patients.
- Differential diagnoses include relative polycythaemia (↓ plasma volume, e.g. dehydration) and polycythaemia due to ↑ erythropoietin (e.g. high altitude).

Essential thrombocythaemia

Characterized by platelet count persistently >500 × 10^9/L without an underlying cause (e.g. blood loss, Fe deficiency, infection, inflammation, hyposplenism, malignancy). 50% of patients are asymptomatic, 25% have splenomegaly, and 25% have a history of thrombosis. Platelet function may be abnormal, esp. in those with platelets >1000 × 10^9/L. Treat with aspirin unless contraindicated. Patients at high risk of thrombosis (e.g. age >60yrs) should also be given hydroxycarbamide to ↓ platelet count to normal range.

Chronic myeloid leukaemia (CML)

Clonal haematopoietic disorder characterized by expansion of mature myeloid cells. It is caused by a chromosomal translocation (Philadelphia chromosome). The median age is 50–60yrs, but can present in childhood. Patients often asymptomatic initially; later, transformation → blast crisis (acute leukaemia) occurs. Continuous treatment with tyrosine kinase inhibitors can → long-term control, but they are costly and regular monitoring is required. The Glivec® International Patient Assistance Program can provide tyrosine kinase inhibitor for free given certain conditions. Otherwise, hydroxycarbamide can be used to ↓ WBC in chronic phase. It is only curable with bone marrow transplantation.

Splenomegaly

The spleen is a major site of antigen presentation and platelet reservoir. Splenic macrophages remove damaged or old RBCs. The spleen enlarges as a result of overactivity of any of these processes.

The high prevalence of chronic infection (esp. malaria) as well as haemolytic anaemias in the tropics means that splenomegaly is a common finding. Splenomegaly may → abdominal distension, discomfort, and early satiety. Massive splenomegaly may → pancytopenia.

Hyperreactive malarial splenomegaly (HMS)

Previously called tropical splenomegaly syndrome; occurs very commonly in areas with high malaria transmission, esp. in adults who have taken up residence in the endemic area. HMS is due to an abnormal immune response to malaria → polyclonal lymphoid activation. HMS is difficult to distinguish from lymphoproliferative disorders, hepatosplenic schistosomiasis, and visceral leishmaniasis, which may coexist in the same territory. Once other causes of splenomegaly have been excluded (Box 10.15), HMS is a likely diagnosis. Repeated courses of ACT or prolonged antimalaria prophylaxis (e.g. proguanil 100mg/d for >6mths) may → ↓ spleen size, supporting the diagnosis.

Splenectomy

Indications for splenectomy incl. trauma, haemolytic anaemia, immune thrombocytopenic purpura. Postoperatively, there is an ↑↑ risk of sepsis (overwhelming post-splenectomy infection (OPSI)) from encapsulated bacteria, esp. *Streptococcus pneumoniae*. Risk of OPSI is ~0.5%/yr, and even with good resources, mortality is ~50%, so prevention is essential. If possible, elective splenectomy should be delayed until age >5yrs because of ↑ susceptibility to OPSI. Pneumococcal, meningococcal, and Hib vaccinations should preferably be given >2wks preoperatively; if splenectomy is unplanned, they should be given >2wks postoperatively; re-immunize for pneumococcus every 5yrs. Phenoxymethylpenicillin prophylaxis (500mg bd) should be commenced postoperatively and continued for life. Patients should be educated about the risk of OPSI and seek immediate attention, or start standby broad-spectrum antibiotics, if they develop a fever with fainting or rigors. There is ↑ risk of severe malaria, so long-term malaria prophylaxis (or residence outside a malaria area) should be advised. Immediately post splenectomy, there is a risk of thrombosis because of transient thrombocytosis, or in the case of haemolytic anaemias, a rise in haematocrit.

Box 10.15 Common causes of splenomegaly

- *Infections*: SBE, brucellosis, typhoid, miliary TB, EBV, CMV, HIV, rubella, hepatitis B, toxoplasmosis, malaria (including HMS*), visceral leishmaniasis*, schistosomiasis*, histoplasmosis, splenic abscess.
- *Malignancies*: lymphoma*, ALL, CLL*, metastatic carcinoma, multiple myeloma, myeloproliferative disorders*.
- *Autoimmune*: SLE, rheumatoid arthritis (Felty's syndrome).
- *Reactive*: autoimmune haemolytic anaemia, haemoglobinopathies*.
- *Congestive*: portal hypertension*, cardiac failure.
- *Other*: sarcoidosis, lipid storage disorders, histiocytosis.

* Can give massive splenomegaly 10cm below costal margin.

Box 10.16 Causes of DIC in tropical countries

- *Infection*: meningococcal, pneumococcal, staphylococcal, Ebola, Marburg, dengue, Lassa fever, malaria (rarely).
- *Malignancy*: disseminated cancer, acute leukaemia.
- *Tissue damage*: burns, fulminant hepatitis, pancreatitis, rhabdomyolysis, fat embolism.
- *Envenoming*: snake bite, *Lonomia* caterpillars (Brazil).
- *Obstetric*: septic abortion, *abruptio placentae*, amniotic fluid embolus, pre-eclampsia/eclampsia, retention of dead fetus.
- *Immune*: ABO-incompatible blood transfusion.
- *Vascular*: vasculitis, malignant hypertension, atrial myxoma.

Disorders of haemostasis

Abnormal bleeding results from disorders of 1° homeostasis (vascular endothelium and platelets) → bleeding into the skin and mucous membranes, or of 2° haemostasis (coagulation and fibrinolytic pathways) → haemorrhage in deep tissues.

Disorders of primary haemostasis

- Vascular purpura: infections, long-term steroid therapy, and vasculitis. In immunocompromised patients, HSV, VZV, and arboviruses (O'nyong'nyong, chikungunya) can → fatal haemorrhage.
- Defective platelet function: can result from drugs (e.g. NSAIDs, aspirin) and complicate some of the haemorrhagic fevers (e.g. Lassa, dengue, Marburg, Ebola), alcoholism, cirrhosis, uraemia, paraproteinaemias, leukaemias, and myeloproliferative disorders.
- Thrombocytopenia: may result from defective production, ↑ destruction/consumption, and splenic pooling (e.g. malaria, visceral leishmaniasis, HIV).

Onyalai Means 'blood blister' and is a thrombocytopenic disorder of unknown aetiology occurring in central southern Africa.

Clinical features Recurrent haemorrhagic bullae on mucous membranes, epistaxis, hypotension, and GI/cerebral haemorrhage. Mortality is 3–10%.

Management Includes blood and platelet transfusion; steroids and IVIg have been used to ↑ platelet count.

Management of bleeding due to thrombocytopenia/ defective platelet function

- Treat underlying causes of thrombocytopenia.
- Desmopressin for uraemic platelet dysfunction.
- Tranexamic acid for mucosal bleeding.
- Platelet transfusions, where available, may be necessary for acute bleeding. Their effect only lasts a few days, and they may be ineffective if peripheral consumption is the cause.

Immune thrombocytopenia often occurs after a viral infection in children and remits spontaneously. Adults may have a more protracted course. Hb and WBC count and blood film should be normal, unless severe bleeding. Other causes of thrombocytopenia should be excluded (Box 10.17). Treatment is usually only for bleeding complications in children, or adults at high risk of bleeding: prednisolone (1mg/kg od for at least 4wks) or IVIg (0.4 g/kg over 5d or 1 g/kg over 2d). Only consider platelet transfusion if severe bleeding complications.

Disorders of secondary haemostasis

Can be congenital, e.g. haemophilia A (factor VIII deficiency), haemophilia B (Christmas disease, factor IX deficiency), and von Willebrand's disease or acquired 2° to malabsorption (→ vitamin K deficiency), liver disease, DIC, and snake envenoming.

Box 10.17 Causes of thrombocytopenia

- ↓ *platelet production*: infections (e.g. typhoid, brucellosis, rubella, mumps, hepatitis C, HIV), megaloblastic anaemia, alcoholism, marrow infiltration or failure (e.g. leukaemia, aplastic anaemia, drugs/chemicals).
- ↑ *peripheral platelet consumption*: infections (e.g. malaria, visceral leishmaniasis, trypanosomiasis, dengue, and other arboviruses, EBV, CMV, Marburg virus), hypersplenism, pregnancy, chronic hepatic disease, DIC, microangiopathic haemolytic anaemia, ITP, onyalai, acute viral infection, AIDS, drugs (e.g. quinine, penicillin, valproate), lymphomas, CLL.

Congenital disorders of haemostasis

Clinical features

Haemophilia is an X-linked deficiency of factors VIII or IX → prolonged APTT and a spectrum of clinical severity. Boys may present with haemorrhage after surgical interventions, spontaneous bleeding into joints and muscles, → crippling arthropathy and deformity of the limbs. Cerebral haemorrhage and spontaneous intra-abdominal or upper respiratory tract bleeding may also occur. Von Willebrand's disease results from a defect in von Willebrand factor → bleeding from mucous membranes because of a defect in platelet function.

Management

General

Refer to a specialist. Avoid NSAIDs, aspirin, and IM injections. Spontaneous musculoskeletal bleeds can be managed with rest, ice, elevation, analgesia, and gentle physiotherapy once acute symptoms settled. Tranexamic acid 25mg/kg oral tds can help mucosal bleeding. Fibrin glue is helpful to control intraoperative bleeding. Vaccinate against hepatitis B, screen for other infections especially HCV, HIV if the patient is receiving plasma-based products.

Specific

Recombinant factor replacement very costly, so plasma-derived, on-demand treatment is more common in resource-poor countries. Severe haemophilia A requires factor VIII concentrate and haemophilia B factor IX concentrate. These products should be virally inactivated and freeze-dried, have a defined activity, and come from a low-risk donor pool. Cryoprecipitate (haemophilia A), cryosupernatant (haemophilia B) or FFP should only be used as a last resort. Desmopressin (0.3–0.4mg/kg/every 12–24h IV in 50mL 0.9% saline over 20min) is effective in some haemophiliac patients. The World Federation of Haemophilia is an excellent resource: http://www.wfh.org.

Acquired coagulation disorders

Vitamin K is a co-factor for coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S. These factors are produced in hepatocytes and deficiency of vitamin K, as well as liver failure can → coagulopathy. Vitamin K deficiency results from small bowel fat malabsorption, biliary or pancreatic dysfunction, starvation, or prolonged antibiotic use.

Vitamin K antagonism Warfarin is a competitive inhibitor of vitamin K. Overdose, sepsis, poor vitamin K intake/absorption, or simultaneous administration of potentiating drugs may → bleeding. For emergency reversal of warfarin, give vitamin K 5–10mg (300 micrograms/kg up to 10mg for children) IV and prothrombin complex 15mL/kg, where available, or FFP 15mL/kg if not.

Liver disease Bleeding is due to a combination of ↓ clotting factor synthesis, thrombocytopenia, platelet dysfunction, vitamin K deficiency, DIC, and dysfibrinogenaemia and should be treated by IV vitamin K, FFP, and cryoprecipitate if fibrinogen is low.

Disseminated intravascular coagulation Results from activation of coagulation pathways in the vasculature and a cycle of consumption of coagulation factors and their inhibitors. May be asymptomatic or associated with bleeding, skin purpura, microangiopathic haemolytic anaemia, and arterial or venous thromboses. Depletion of all coagulation factors → prolongation of APTT and PT, ↓ fibrinogen and platelets, and RBC fragmentation on blood film. See Box 10.16.

Management Treat the underlying condition, careful monitoring, give blood products as required. If there are predominantly thrombotic complications, consider cautious anticoagulation with IV heparin.

Box 10.18 Paediatric note: haemorrhagic disease of the newborn (HDN) or vitamin K deficiency bleeding (VKDB)

Neonates are vitamin K deficient because of poor placental transfer and ↓ hepatic synthesis. This can → early bleeding (e.g. intracranial haemorrhage) in the 1st week of life, but bleeding may also occur later. At-risk groups incl. preterm infants and infants of mothers on anti-TB therapy, anticonvulsants, or warfarin. Vitamin K levels are low in breast milk and breastfed infants are at ↑ risk of late-onset VKDB at 1–3mths.

VKDB can be prevented with routine prophylaxis of vitamin K. Both oral and IM preparations are available, but IM vitamin K prevents both early- and late-onset VKDB. For routine prophylaxis at birth, give 1mg vitamin K IM (preterm 400 micrograms/kg, max. 1mg). Babies at high risk of VKDB should receive prompt IM vitamin K administration after delivery.

Treatment of VKDB is with 1–2mg parenteral vitamin K plus FFP if there are bleeding complications.

Laboratory issues

Most 1° level health centres usually have a light microscope, e.g. for diagnosis of TB and malaria. This enables several important investigations (e.g. WBC and platelet count, RBC morphology, differential WBC%). However, the microscopist should spend <4h/d looking down the microscope to avoid fatigue and poor-quality reporting.

The following principles can ↓ errors in tests:

- Use accurate volumes.
- Check date, dilution, and storage of reagents.
- Keep instruments and cuvettes clean and grease/dust free.
- Keep colorimeters away from sunlight.
- Collect capillary or venous blood samples correctly and use appropriate amount of anticoagulant.
- Use correct centrifuge times and speeds.
- Filter stains/diluting mixtures; check for particles and use correctly buffered water.
- Run samples in duplicate.
- Use clean, dry slides.
- Fix slides with water-free methanol when completely dry.
- Consult the standard operating procedures for each test.

Some basic principles of laboratory management

Range of tests

Better to provide a few essential tests to high standards than a wide range of poor-quality tests. Test selection should take into account sensitivity and specificity of tests, as well as +ve and –ve predictive values (influenced by disease prevalence in local population), reliability, availability of reagents and consumables, cost, safety, sustainability, and skills of laboratory staff.

Management and operation of equipment

Ensure regular maintenance, availability of manuals, adequate space and light, and reliable supplies of consumables/reagents. Minimize dust and heat. Laboratory staff should be trained and supervised and carry out tests within their skills and knowledge.

Quality control

Simple ways of promoting confidence in test results include independent reanalysis of selected slides or samples within one laboratory, or regular exchange of samples with neighbouring laboratories.

For a typical quality control exercise, during a defined period ask laboratory to keep all positive slides and 10% of negative slides for quality control checking.

Include known positive samples within a batch of tests to demonstrate that the test is working (e.g. a blood sample known to contain HbS can be included in each batch of sickle cell screening tests); or use of reference samples.

Standard operating procedures (SOPs)

These are detailed descriptions of laboratory tests designed to prevent errors and ensure consistent results. They must be designed for the local situation, kept up to date, and adhered to by all staff. SOPs provide an excellent teaching resource. For each test, they should include:

- The principle of the test and valid reasons for requesting it.
- Details of the specimen required and how it should be collected.
- The equipment and reagents needed, as well as information on how to maintain, procure, and store them.
- The method of the test.
- Quality control measures and sources of error.
- Safety considerations.
- The procedure to be followed in reporting the results (e.g. units to be used).

Chapter 11

Endocrine disorders

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Diabetes mellitus

General points

- Diabetes mellitus (DM) is caused by absolute/relative insulin deficiency or ↓ insulin action, or both; it is characterized by hyperglycaemia and associated with deranged metabolism of carbohydrate, fat, and protein.
- DM has been classified pathophysiologically into a number of types and used by clinicians to guide treatment at diagnosis and when glycaemic control is poor.
- However, there is ↑ awareness that some individuals can't be clearly classified as type 1 (T1DM) or type 2 diabetes mellitus (T2DM) at diagnosis—there is overlap in the types of diabetes. Inability to classify the type of diabetes should not delay treatment, if an individual is symptomatic. The major types are currently as follows:

T1DM

This may be immune-mediated or idiopathic. Characterized by β-cell destruction and subsequent need for insulin therapy for survival. Classically occurs in children but also in adults. Patients are prone to ketoacidosis. If autoimmune pathogenesis, may be associated with other autoimmune diseases in patient/family.

T2DM

This is due to a progressive loss of β-cell insulin secretion usually on a background of insulin resistance. Accounts for >90% of cases of DM globally; greatest number of people with T2DM in LMICs. Earlier age of onset is being seen, sometimes in childhood.

Gestational diabetes mellitus

This is DM diagnosed in the 2nd or 3rd trimester of pregnancy that was not overt DM prior to gestation.

Secondary diabetes

Due to: drugs (steroids, thiazide diuretics, ART), pancreatic disease (chronic pancreatitis, tropical calcific pancreatitis, post-surgery), endocrine disease (Cushing's, acromegaly, phaeochromocytoma), single gene disorders usually affecting insulin secretion (also known as maturity diabetes of the young).

Clinical presentation

DM may present:

- *Acutely*: ketoacidosis, ↓ weight, polyuria, polydipsia. (If blood glucose normal, consider hypercalcaemia and diabetes insipidus as rarer causes of polyuria and polydipsia.) Classically a first presentation for DM with ketoacidosis was thought to be indicative of T1DM but increasingly patients, esp. adults who present with ketoacidosis, who are overweight or have signs of acanthosis nigricans and a FHx of DM are later found to have T2DM.
- *Subacutely*: as for acute, but occurring over a longer time, plus lethargy, infection (e.g. pruritus vulvae, furunculosis).
- *Chronically*: may present with complications—infection, cataract, microangiopathy (retinopathy, neuropathy, nephropathy) and macroangiopathy (stroke, MI, claudication), foot ulcers.

Diagnosis

- DM can be diagnosed based on a single abnormal fasting or random plasma glucose level or HbA1c in symptomatic individuals. Two abnormal tests are required for diagnosis in the absence of symptoms.
- The diagnostic cut points are:
  - Fasting plasma glucose ≥7.0mmol/L.
  - Random plasma glucose ≥11.1mmol/L.
  - HbA1c ≥6.5%.
- An oral glucose tolerance test is seldom required in clinical practice, except in pregnancy.

Impaired fasting glucose

Defined as a fasting plasma glucose 6.0–6.9mmol/L and is associated with ↑ risk of IHD and progression to diabetes. Lifestyle modification may delay/prevent progression to diabetes. Need to address other risk factors for IHD (e.g. obesity, lipids, smoking, aspirin).

Management of diabetes mellitus

General points

- Empowering people with diabetes to engage in their care is central to DM management, while successful self-management is key to ensure that treatment and quality of life goals are achieved.
- DM education should enable the patient to: choose healthy options (incl. avoiding all fruit juices, sugar sweetened drinks, and processed food; ↑ physical activity; tobacco cessation; management of weight; and strategies for coping with stress); take medications and self-monitor glucose if necessary; prevent and manage hypoglycaemia; take care of their own feet; request screening for complications.
- Women of child-bearing age require counselling to optimize their health and glycaemic control before conception. Once pregnant they need to be referred for specialist care as poor glycaemic control is associated with ↑ risk of miscarriage, ↑ fetal abnormality, and ↑ birth complications.

Prevention of complications

- People living with DM are at ↑ risk of microvascular (retinopathy, nephropathy, and neuropathy) as well as macrovascular complications incl. stroke, IHD, and peripheral vascular disease.
- Good glycaemic control has been shown to ↓ microvascular disease, while a multifactorial approach including glycaemic, BP, and lipid control can → macrovascular benefit.
- Further risk factor modification includes smoking cessation in all patients and aspirin if there is a history of IHD or previous stroke. Statins should be added in most patients with T2DM >40yrs old and in all patients with established cardiovascular disease or chronic kidney disease, irrespective of their lipids.
- Health providers play a pivotal role in screening for complications, institution of appropriate interventions (e.g. foot care advice for people with 'at risk' feet) and referral (e.g. for consideration of laser therapy for pre-proliferative and proliferative retinopathy).

Treatment targets for glycaemia, BP, and lipids

- Glycaemic control needs to be individualized: HbA1c <7% for most patients, 7.5–8.5% if history of IHD/limited life expectancy, multiple comorbidities, severe vascular disease, advanced chronic kidney disease, recurrent severe hypoglycaemia/hypoglycaemic unawareness. Fasting glucose 4–7mmol/L, post-meal glucose 5–10mmol/L.
- BP: <140/80mmHg in most patients (<130/80mmHg in patients at ↑ risk of stroke).
- Lipids: total cholesterol <4.5mmol/L; triglycerides <1.7mmol/L; HDL >1.0mmol/L in men and >1.2 in women; LDL <1.8mmol/L.

Drug therapy

Treatment depends on the type of DM, drug availability, as well as potential benefits and side effects profiles. Patients with T2DM may be managed with oral therapy initially but many will eventually require insulin. Insulin is indicated in T1DM.

Treatment approach in T2DM

Step 1: monotherapy

In uncomplicated, newly diagnosed T2DM, lifestyle intervention (diet and ↓ weight) plus metformin remain the cornerstones of treatment.

Metformin should be started at 500mg daily and slowly titrated upward to avoid GI side effects (max. dosage 2g daily). Metformin is contraindicated in severe renal, liver, or heart failure.

Step 2: dual oral therapy

If glycaemic control not adequate after 3mths, a second oral agent, usually a sulfonylurea (e.g. gliclazide 40–160mg daily or glimepiride 1–4mg daily) should be added. Sulfonylureas work by ↑ insulin secretion, → hypoglycaemia is the main side effect. HbA1c should be checked every 3mths and doses of medications titrated until target is reached.

Step 3: add-on insulin therapy

Patients still hyperglycaemic despite two oral agents require insulin. Insulin should also be used in any patients presenting with severe hyperglycaemia (HbA1c >10%, fasting glucose >14mmol/L, random glucose >16.5mmol/L, weight loss, and ketosis).

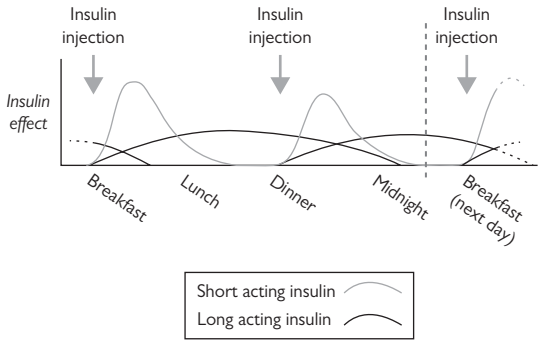

Fig. 11.1 Balancing insulin action and meals. How to monitor and adjust insulin doses with a typical twice-daily regimen of short- and long-acting insulin suitable for a type 1 diabetic. Before breakfast and main evening meal a mixture of short-acting insulin and long-acting insulin is injected. Risk of hypoglycaemia max. at mid-morning and pre-bed, so snacks essential at these times. Check glucose before each meal and at bedtime, and adjust doses accordingly.

Insulin

Knowledge of insulin profiles in terms of onset of action, peak, and duration of action is necessary when prescribing therapy (Table 11.1).

- Treatment regimens vary, depending upon type of DM, availability of insulins, access to home monitoring, and lifestyle. The typical daily requirement for insulin is 0.5–1.0U/kg/d (pre-pubertal children 0.6–0.8U/kg/d) in divided doses.
- Whenever starting insulin in T1DM or T2DM start with 0.2–0.4U/kg/d and adjust the dose at subsequent reviews.

Table 11.1 Insulins choice in DM

Type	Onset of action	Peak	Duration
Short-acting regular human insulins	30–60min	2–3h	7–8h
Intermediate-acting (basal) human insulins Neutral protamine Hagedorn (NPH)	120–240min	4–10h	10–18h
Pre-mixed human (biphasic) insulins 30% regular + 70% NPH	30–60min	Dual peak	10–18h

- T1DM requires insulin action through 24h, whereas insulin-treated T2DM may be controlled with a single injection of medium-acting insulin once or twice per day.

For T1DM there are two widely used regimens

- *Two injections/day*: start with 0.4U/kg/d, 2/3 given in morning and 1/3 in evening. A premixed/biphasic insulin is usually used (30% short acting + 70% intermediate acting) but separate short- and intermediate-acting insulin can be mixed using needles and vials. Insulin injections should be given 30min before breakfast and evening meal. Avoiding hypoglycaemia relies on three regular meals a day and two snacks, one mid-morning and one before bed (Fig. 11.1).
- *Basal/bolus*: single injection of long-acting at bedtime (basal) and three injections of soluble during the day (bolus) before each meal. Start with a total daily dose of 0.4IU/kg/d with 50% long-acting insulin and 50% short-acting insulin divided over three meals. The dose of long-acting insulin can be titrated by 2U every 3d to optimize the fasting glucose, while the mealtime doses can be adjusted according to the pre-meal glucose and food intake.

Two injections/day involves fewer injections, but is less flexible and means regular meal times and injection times must be adhered to. Basal/bolus allows for more flexibility, but requires more injections and is most effective if home blood glucose monitoring can be done.

For T2 DM

- Insulin can be initiated using bedtime (basal) dose of intermediate- or long-acting insulin. It is convenient to start with 10U and monitor the fasting plasma glucose and titrate to achieve values of 4–7mmol/L before breakfast by ↑ the dose every 3d by 2U. A bedtime snack is advised to avoid nocturnal hypoglycaemia.
- A two-injection per day regimen using biphasic insulin as for T1DM can also be considered if post meal glucose values are very high.

Diabetic treatment with intercurrent illness

Never stop insulin in T1DM patients—even if they are unable to eat or drink. The stress of illness ↑ insulin requirements. However, oral intake is often poor so it is important to monitor blood sugar levels, 4× a day if possible. Drink plenty of water and, if unable to eat, replace meals with frequent, small drinks, e.g. soup, fruit juice or milk. If poor calorie intake, ↓ long-acting insulin or biphasic insulin by 20%. Short-acting insulin may need to be given/altered depending on blood glucose levels. It is important that patients with T2DM on insulin also continue their basal insulin during periods of intercurrent illness.

IV insulin regimens

IV insulin may be required, e.g. diabetic ketoacidosis or acutely unwell patients unable to take/absorb oral hypoglycaemics or whose blood glucose is too unstable to control with regular SC insulin. Careful control of blood glucose with IV insulin may improve the outcome of critical illness including acute coronary syndromes. IV insulin may be given either as a sliding scale or as a glucose–K^+–insulin (GKI) infusion.

Insulin sliding scale IV infusion

Make 50U of soluble insulin up to 50mL with normal saline (i.e. 1U/mL solution). Measure blood glucose hourly and infuse at a rate according to the blood glucose in Table 11.2. Individual sliding scales vary between institutions, and can be adjusted for individual patients.

GKI infusion

Add 15U of soluble insulin to a bag of 500mL 10% glucose with 20mmol K^+. Infuse at 100mL/h and check the blood glucose hourly. Make up new bags with altered insulin units as shown in Table 11.3. Unless the blood glucose is quite stable, the GKI regimen tends to be more wasteful as new bags need to be made up frequently.

Table 11.2 Insulin sliding scale IV infusion: 50mL normal saline containing 50U soluble insulin (1U/mL solution)

Blood glucose (mmol/L)	Units/h
<5.0	1
5.1–12.0	3
12.1–20.0	4
>20.0	6

Table 11.3 Glucose–K^+–insulin (GKI) infusion: insulin added to 500mL 10% glucose with 20mmol K^+. Infuse at 100mL per hour

Blood glucose (mmol/L)	Insulin in bag (units)
<5	6
5–15	15
>15	25

Diabetic follow-up

Organized care for people living with diabetes is essential in order to:

- Promote diabetes education and self-management.
- ↑ adherence to treatment.
- Encourage weight management through diet and exercise.
- Prevent and monitor development of long-term complications.
- Evaluate treatment targets: HbA1c, BP, and lipids.

Clinic checklist

Follow up every 3–6mths, depending on degree of control. Certain examinations occurring at every visit and others annually as outlined in Table 11.4.

Table 11.4 Follow up of patients with DM

	Every 3–6mths	Annual assessment
History		
Symptoms of hyperglycaemia	X	X
Episodes of hypoglycaemia	X	X
Treatment adherence	X	X
Lifestyle factors: Weight Diet Smoking Physical activity	X	X
Symptoms of complications	X	X
Symptoms of depression	X	X
Physical examination		
Weight	X	X
Height	X	X
Waist circumference	X	X
BP	X	X
Foot assessment: Pulses Monofilament Vibration Ankle jerks		X
Eye exam: Visual acuity Fundoscopy		X
Injection sites (when applicable)	X	X
Cardiovascular examination		X

	Every 3–6mths	Annual assessment
Special investigations		
HbA1c	X	X
Cr & K^+		X
Lipogram		X
Urine dipstick (glucose/ketones/protein)	X	X
Urine microalbumin		X
ECG		X

Nephropathy

- If abnormal screening test: confirm by repeat testing of estimated GFR (calculated from serum Cr) within 3mths, and urine albumin/creatinine ratio (ACR) measurements.
- If either estimated GFR remains low, or two of three random urine ACRs are abnormal, then diagnosis of CKD is confirmed. No need to repeat urine ACR if ↑↑ albuminuria.
- Good BP control can ↓ progression of renal dysfunction. Use ACE inhibitor or ARB drugs and check serum Cr and potassium 1–2wks after initiation or titration of a renin–angiotensin–aldosterone system blocker as may cause rise in both.

Diabetic ketoacidosis (DKA)

DKA is a hyperglycaemic emergency characterized by:

- Hyperglycaemia: glucose >13.9mmol/L.
- Acidosis: pH <7.3 or bicarbonate <18mmol/L.
- ↑ ketones (blood and urine).

DKA can occur with both T1DM and T2DM and is commonly precipitated by infections, stopping of insulin therapy, MI, and stroke.

Clinical features

Symptoms typically include a few days of polyuria, polydipsia, vomiting, weakness, and abdominal pain.

Acidotic (Kussmaul's) breathing, dehydration +/− shock together with clinical features of a cause (e.g. UTI may be found).

Investigations

Glucose, FBC, U&E, ECG, bicarbonate, blood gases, infection screen (urine and blood cultures, CXR). Look for ketones in the urine (or in blood if available).

Management of DKA in adults

(For different management of DKA in children and adolescents see ➲ Box 11.1, p. 494.)

- Urgently correct dehydration (may be life-threatening), e.g. normal saline 1–2L/h for the first 2h, then 250–500mL/h thereafter. IV fluids should be switched to 5% glucose once the serum glucose <14mmol/L and the patient is still requiring IV insulin for DKA management to avoid hypoglycaemia.
- Insulin therapy: short-acting IV insulin as a continuous infusion (0.14U/kg/h) is preferable in an intensive care/high care setting. If ICU care is not available, alternatives include 10U of regular insulin IM or IV hourly.
- K^+: if the initial K^+ is <3.5mmol/L, start replacement before insulin infusion to avoid severe hypokalaemia and its complications of arrhythmias or respiratory muscle weakness. Measure K^+ 4hrly. Initial K^+ often high, but ↓ rapidly with insulin: if rapid K^+ measurement not available give 20mmol K^+/L in the second and subsequent litres of fluid (unless oliguric, when K^+ may need to be withheld), and then maintenance and replacement K^+ according to blood levels.
- Monitor vital signs and blood glucose every hour.
- Prevent complications, including aspiration, DVT. Pass NGT to decompress stomach. Be alert to shock, cerebral oedema, and DIC.
- If available give 5000IU heparin SC bd or low-molecular-weight heparin.
- Giving bicarbonate is unnecessary. Insulin and fluid will correct acidosis provided the underlying cause (e.g. infection) is treated. If there is gross acidosis without ketosis, consider renal failure, aspirin overdose, or lactic acidosis.
- Identify and manage the precipitant, e.g. poor compliance with treatment, intercurrent illness.

Hyperglycaemic hyperosmolar non-ketotic coma (HONK)

Hyperglycaemic hyperosmolar non-ketotic coma generally affects older individuals with T2DM. HONK is characterized by a gradual onset of severe hyperglycaemia, hyperosmolality, often >320mmol/L, and dehydration. There is little or no ketonuria or acidosis.

Treat as for ketoacidosis, but correct the osmolality slowly (over 2–3d) using half normal or normal saline to avoid cerebral oedema after large fluid shifts. DVT is a risk, so use heparin prophylaxis. Seek an underlying cause, e.g. infection, silent MI.

Hypoglycaemia

Hypoglycaemia is common, and important in individuals with DM treated with insulin and/or insulin secretagogues. Clinically significant hypoglycaemia is <3.0mmol/L; severe hypoglycaemia is any low blood glucose associated with cognitive impairment and requiring intervention. Recurrent hypoglycaemia → hypoglycaemic unawareness → considerable anxiety to those affected.

Causes

An imbalance between insulin and glucose, most commonly due to excess insulin or insulin secretagogue (sulfonylurea) for the patient's food intake or exercise.

Presentation

Autonomic: sweating, anxiety, tremor, tachycardia, palpitations; altered behaviour, inability to concentrate, headache. Rarely, seizures and coma of rapid onset.

Management

- If unable to take sugar orally, give IV glucose (e.g. 25–50mL of 50%) followed by a saline flush to avoid damaging the vein. May also use larger volumes of 10% or 20% glucose.
- Improvement should be rapid. If not, repeat and continue 10% dextrose in water by IV at a rate of ~1L over 6h, to prevent recurrent hypoglycaemia, esp. if induced by long-acting insulin and/or a sulfonylurea—these patients need monitoring for up to 48h. This should be followed quickly by feeding with complex carbohydrate.
- If IV access fails/not available, give glucagon 0.5–1mg IM. Repeated doses of glucagon become ↓ effective as glycogen stores become depleted.
- Review medication and educate to prevent recurrences.
- If patient has lost awareness of hypoglycaemia, → frequent self-monitoring of blood glucose, review medications, and if possible refer to specialist.

Diabetes in children and adolescents

- If possible, refer or discuss children and adolescents with DM to a paediatric diabetes specialist.
- Diagnostic criteria same as for adults.
- T1DM diagnosis is most likely, even if obese. T2DM (obese with acanthosis nigricans) is associated with ↑ autoimmune beta cell destruction and a risk of ketoacidosis.
- If available, check antibodies in children and adolescents who appear T2DM, as positive antibodies are associated with sooner insulin requirements (and risk of ketoacidosis).
- Always discuss very young diabetics (<1yr) with a paediatric diabetes specialist. Monogenic diabetes, caused by a single gene mutation, should be considered in the very young, as therapy may be different.
- Insulin regimens need to be individualized, with consideration given to the activities and feeding habits of the young child. While school-going children may benefit from regimens consisting of regular and NPH insulin, consider rapid analogue insulin for meals in young children and those with irregular or fussy eating habits, as these can be given after intake of carbohydrates.
- Consider long-acting basal analogues if nocturnal hypoglycaemia occurs and bed-time snacks are not avoiding NPH-associated lows.

See Box 11.1 for management of DKA in children and adolescents.

Box 11.1 Management of DKA in children and adolescents

Children with DKA are high risk, and can die of cerebral oedema, hypokalaemia, or aspiration pneumonia. Seek senior advice on presentation and follow local guidelines. See: https://www.bsped.org.uk/clinical-resources/guidelines.

Resuscitate (ABC) if necessary (inside front cover of this handbook). Give 10mL/kg fluid boluses only if shocked (up to 30mL/kg).

Clinical features, diagnosis, and investigations

Similar to adults.

Factors which may need intensive care

- Severe acidosis; pH <7.1 with marked hyperventilation.
- Severe dehydration with shock.
- ↓ conscious level (*note*: risk of aspiration from vomiting).
- Young age (<2yrs).
- Insufficient staffing to allow adequate monitoring.

Rehydrate

- Calculate fluid requirements over the first 48h as deficit (based on degree of dehydration) plus maintenance. Start fluids 1h before insulin infusion to ↓ risk of cerebral oedema. After 12h may switch from 0.9% to 0.45% saline if Na^+ stable or ↑.
- Insulin infusion is usually started at 0.1U/kg/h:
  - When glucose <14mmol/L add glucose to fluid (e.g. 0.9% saline + 5% glucose); continue insulin to switch off ketogenesis.

  - When blood pH is >7.3, blood glucose is <14mmol/L and the fluids contain glucose consider ↓ insulin infusion rate, but no less than 0.05U/kg/h.
- If ketosis not resolving, increase the insulin by 25% and increase the infused glucose to 10% if the BG goes lower than 8mmol/L.
- Replace K in all fluids given after initial resuscitation (unless anuric): e.g. 500mL 0.9% saline + 20mmol KCl; adjust according to electrolyte levels where results are available.

Monitor closely

Hourly observations including fluid status, GCS, blood glucose, and electrolytes.

Resolution of DKA

Change to SC insulin when feels well, able to eat and drink, acidosis resolved, blood ketones <1mmol/L or urinary ketones falling. Discontinue insulin infusion 60min (if soluble or long-acting insulin) or 10min (rapid-acting insulin) after the first SC injection to avoid rebound hyperglycaemia.

Hypoglycaemia treatment in children and adolescents

- If able to take safely: 10–20g of rapidly absorbable glucose by mouth.
- If unable to take orally: give 2mL/kg of 10% glucose IV, repeated if necessary, followed by feeding of complex carbohydrates, or if poor oral intake, followed by maintenance IV fluid with 10% glucose.
- 50% glucose is *not* used in children and adolescents because of the risk of hyperosmolality as well as tissue damage from extravasation.
- Glucagon (0.5mg for children <8yrs old or <25kg), if IV access not possible.

Hypothyroidism

Causes

- *Common*: autoimmune, iodine deficiency, iatrogenic (surgery or radioactive iodine).
- *Less common*: drugs (e.g. lithium, amiodarone, iodine), thyroiditis, autosomal recessive defect.

Clinical features

Symptoms

- *Common*: weight gain, fatigue, constipation, dry skin, hoarse voice, menorrhagia, depression, cold intolerance.
- *Uncommon*: dementia, cerebellar ataxia, myopathy, angina, galactorrhoea.

Examination

- *Common*: coarse features, bradycardia, goitre, delayed reflexes, loss of the outer third of the eyebrows.
- *Uncommon*: hypothermia, congestive cardiac failure, pleural effusion, pericardial effusion.

Diagnosis

- If thyroid-stimulating hormone (TSH) is elevated then request a free thyroxine (fT4). A free triiodothyronine (fT3) and antithyroid antibodies are not usually required.
- *Overt 1° hypothyroidism*: ↑ TSH, ↓fT4.
- *Subclinical hypothyroidism*: ↑ TSH, normal fT4, and normal fT3.
- *Secondary hypothyroidism*: normal or ↓ TSH, low fT4.

Management

Start with a dose of 50–100 micrograms levothyroxine daily, increasing up to 1.6 micrograms per kg. In the elderly or patients with ischaemic heart disease or cardiac failure start with 25 micrograms daily.

Adjust the dose of levothyroxine every 4–8wks while monitoring the TSH. Routine use of T3 is not recommended.

Subclinical hypothyroidism

- If TSH is >10mIU/L then treat with levothyroxine.
- If TSH is 4.0–10mIU/L then measure antithyroid peroxidase and antithyroglobulin antibodies: if positive, then consider treatment; if negative, consider treatment in pregnancy, dyslipidaemia, depression, going for surgery.
- Repeat the TSH in 2–3mths if no treatment started.

Secondary hypothyroidism

- Exclude hypoadrenalism before commencing levothyroxine.
- Use the fT4 level (not TSH) to guide levothyroxine replacement and attempt to keep the fT4 level in the upper-normal range.
- Refer to a specialist.

Hypothyroidism in pregnancy

- Ensure that the patient is euthyroid before conception.
- ↑ dose of levothyroxine by 25% as soon as the patient is pregnant.
- Measure TSH monthly and adjust the dose of levothyroxine to keep the TSH normal for the trimester.
- Manage patient with an obstetrician and/or an endocrinologist.

Hyperthyroidism

Causes

- *Common*: Graves' disease, multinodular goitre, thyroiditis, single toxic nodule.
- *Less common*: drugs (e.g. lithium, amiodarone), thyrotoxicosis factitia, struma ovarii, gestational trophoblastic disease, hyperemesis gravidarum.

Clinical features

Symptoms

- *Common*: weight loss, anxiety, emotional lability, sweating, insomnia, tremulous, palpitations, amenorrhoea, heat intolerance, hair thinning, diarrhoea.
- *Uncommon*: angina, gynaecomastia.

Examination

- *Common*: sweaty, fidgety, anxious, lid lag, lid retraction, palmar erythema, tachycardia, atrial fibrillation, goitre, brisk reflexes, proximal muscle weakness.
- *Graves' disease*: diffuse goitre with a bruit, eye changes, pretibial myxoedema, acropachy (finger clubbing).
- *Thyroiditis*: tender thyroid.
- *Uncommon*: congestive cardiac failure.

Diagnosis

If TSH is low, request fT4. fT3 and antithyroid antibodies not required.

- *Hyperthyroidism*: ↓ TSH, ↑ fT4.
- *Subclinical hyperthyroidism*: ↓ TSH, normal fT4 and fT3.

In patients with hyperthyroidism, the cause will dictate treatment. Graves' disease is common, confirmed by TSH receptor antibodies. If these are normal, image the thyroid by isotope scan or USS.

Management

- β-blockers (esp. propranolol) can improve sympathetic symptoms (tremor, tachycardia, sweating).
- ↓ thyroid hormone levels.

Graves' disease

- Option 1: treat for 12–18mths with propylthiouracil (PTU), methimazole, or carbimazole. 40% of patients with Graves' disease will remain euthyroid for >12mths after stopping treatment. Patients unlikely to go into remission if: large goitre, ↑↑ fT4 levels, ↑ TSH receptor antibody levels, males, smokers.
- Option 2: thyroid ablation with radioactive iodine (I^{131}).
- Option 3: total or partial thyroidectomy, esp. if obstructive symptoms (stridor, dysphagia) or severe Graves' eye disease:
  - *Hyperthyroid multinodular goitre*: I^{131}.
  - *Thyroiditis*: usually resolves spontaneously, glucocorticoids or NSAIDs can be used for pain.
  - *Single toxic nodule*: surgery or I^{131}.

Special points

- Warn patients about developing agranulocytosis or cholestatic liver impairment when using PTU, methimazole, or carbimazole.
- Tell the patient to return if they develop a sore throat and fever or jaundice after starting treatment; check WCC, neutrophils, and/or LFTs.

Subclinical hyperthyroidism

- Treat patients who are postmenopausal or >65yrs old and have a TSH persistently <0.1mIU/L.
- Consider treatment if:
  - >65yrs old or postmenopausal women, if the TSH is less than normal but >0.1mIU/L.
  - Premenopausal women and younger patients if the TSH <0.1mIU/L and they have symptoms of hyperthyroidism or coexisting conditions (osteopenia, osteoporosis, or cardiovascular disease).

Enlarged thyroid gland (goitre)

Causes

- *Common*: physiological (endemic: iodine deficiency; sporadic: pregnancy/puberty), autoimmune (Graves' disease, Hashimoto's thyroiditis), de Quervain's thyroiditis, goitrogens (e.g. sulphonylurea drugs, cassava, soya beans), nodular goitre (single or multinodular), tumours (benign or malignant).
- *Less common*: dyshormonogenesis.

Clinical features

- Asymptomatic.
- Symptomatic:
  - Hyperthyroidism: see ➔ Hyperthyroidism, p. 498.
  - Hypothyroidism: see ➔ Hypothyroidism, p. 496.
  - Compression: stridor, dysphagia, altered voice.
- Examination:
  - *Common*: signs of hyperthyroidism or hypothyroidism, palpable nodule/s.
  - *Uncommon*: deviation of the trachea.

Diagnosis

- If TSH abnormal then request a fT4; fT3 and antithyroid antibodies are generally not required.
- If there is a palpable nodule or symptoms or signs of compression do thyroid USS.

Management

- Treat hyperthyroidism/hypothyroidism as outlined previously (➔ Hyperthyroidism, p. 498, and Hypothyroidism, p. 496).
- If there are symptoms or signs of compression or a palpable nodule, refer to a surgical centre.

Pituitary dysfunction

Patients with pituitary hormone dysfunction should be referred to a specialist centre for further evaluation and management. Patients should be encouraged to wear a Medic Alert bracelet or necklace detailing the therapy that they are taking.

Causes

- Pituitary hormone deficiency:
  - *Common*: pituitary adenoma, iatrogenic (surgery, irradiation), idiopathic.
  - *Uncommon*: genetic, infarction (Sheehan's syndrome, apoplexy), invasive (adenoma, craniopharyngioma, brain tumour), infiltrative (sarcoidosis, haemochromatosis, histiocytosis), immunological (lymphocytic hypophysitis), infectious (tuberculosis, syphilis), injury (head trauma).
- Pituitary hormone excess:
  - *Common*: pituitary adenoma.
  - *Uncommon*: ectopic neuroendocrine tumours.

Clinical features

The rapidity of onset and the symptoms depend on the number of hormones that are deficient and the underlying cause.

Symptoms

Patients can present with symptoms and signs of:

- Mass effect (headache, cranial nerve deficits (III, IV, V), visual field defects).
- Hormone deficiency: *growth hormone (GH) deficiency* (↑ weight, fatigue, ↓ energy, ↓ concentration and memory), *hypogonadism* (in women altered menstruation or infertility and in men ↓ sexual function, infertility, ↓ libido and energy), *hypothyroidism* (fatigue, ↑ weight, dry skin, constipation, cold intolerance, depression, mental 'fogginess'), *adrenal hypofunction* (fatigue, weakness, ↓ weight) or symptoms of an underlying cause; diabetes insipidus (polyuria, polydipsia, nocturia, dehydration).
- Hormone excess: *acromegaly* (symptoms may occur slowly over many years and include soft tissue swelling, an ↑ in size of hands and feet, sweating, macroglossia, prognathism and obstructive sleep apnoea); *Cushing's disease* (unexplained ↑ weight, easy bruising, weak proximal muscles, menstrual disturbances, ↓ libido, infertility and psychological disturbances incl. depression); *prolactinoma* (galactorrhoea in women and men; altered menses and infertility in women; ↓ libido, erectile dysfunction, infertility and gynaecomastia in men).

Examination

- Mass effect: visual field defect, cranial nerve III, IV, V palsy.
- Hypersecretion/hyposecretion of a pituitary hormone.

Diagnosis

Each pituitary hormone needs to be evaluated individually: ACTH and cortisol, TSH, GH, serum insulin-like growth factor, prolactin, luteinizing hormone/follicle-stimulating hormone, and antidiuretic hormone.

Management

Pituitary hormone deficiency

Each deficient hormone must be supplemented. GH is not routinely replaced in adults as it is expensive. *Cortisol*—see ➲ Hypoadrenalism, p. 506. *Thyroid hormone*—see ➲ Hypothyroidism, p. 496. *Oestrogen*—for patients <50yrs old the combined oral contraceptive can be used (if no contraindications) and for patients >50yrs old combined hormone replacement therapy (oestrogen and progesterone) can be used. Testosterone—various forms of testosterone replacement.

Pituitary hormone excess

Most patients with Cushing's disease or acromegaly will require surgery while most patients with a prolactinoma can be treated medically with bromocriptine or cabergoline.

Endocrine hypertension

Hypertension may be the result of numerous endocrine disorders, such as pheochromocytoma, hyperaldosteronism, Cushing's syndrome, etc.

Primary hyperaldosteronism

↑ production of aldosterone from the zona glomerulosa, e.g. by an aldosterone-producing adenoma or idiopathic hyperaldosteronism.

Diagnosis

- Consider if spontaneous hypokalaemia and/or resistant hypertension.
- Suspect if refractory hypertension, hypertension <40yrs of age, hypokalaemia.
- If K^+ depletion severe, may have weakness/thirst, polyuria/paraesthesias, metabolic alkalosis.
- ↓ plasma renin and an ↑ aldosterone is suggestive of hyperaldosteronism.

Management

Spironolactone up to 300mg per 24h; referral to specialist centre.

Pheochromocytoma and paraganglioma

General points

- Rare tumours that produce catecholamines.
- 90% arise from adrenal medulla; 10% extra-adrenal.
- Mortality is high if untreated.
- FHx is frequently positive, as often autosomal dominant.
- May be malignant.

Presentation

The clinical presentation of pheochromocytomas and paragangliomas varies widely from no symptoms to catastrophic life-threatening clinical conditions.

- Classic triad of pounding headache, profuse sweating, and palpitations occurs in spells that last from several minutes to 1h.
- May have many vague symptoms, e.g. flushing, pallor, headache, fainting, dyspnoea, headache, palpitations.
- Paroxysmal HT in 35% of cases, may be superimposed on sustained HT, may → hypertensive crisis.

Diagnosis

Elevated plasma or urine metanephrines.

Management

- Treat HT using an α-blocker.
- Avoid β-blocker.
- Referral to a specialist centre.

Cushing's syndrome

Causes

- Iatrogenic Cushing's syndrome from steroids is the commonest.
- ACTH-dependent Cushing's disease is usually from pituitary microadenomas.
- Ectopic ACTH production, e.g. from small cell carcinoma of the lung.
- Rare cases result from tumours, e.g. adrenal adenoma.

Presentation

- ↑ weight gain, irregular periods, hirsutism, muscle weakness, depression, violaceous stretchmarks, easy bruising.
- Rarely: erectile dysfunction, fractures, DM.
- HT in ~80%.
- Bruising and thinning of the skin, proximal muscle weakness.
- Obesity, supraclavicular fat-pads, dorsal fat pads: these are non-specific.

Diagnosis

The diagnosis can often also be very challenging and requires a specialist. Tests are: dexamethasone suppression test, 24h urinary cortisol, or midnight salivary cortisol. Avoid tests for Cushing's syndrome when patients are acutely ill, withdrawing from alcohol or drugs, or suffering from depression as these can cause false +ve results.

Management

- If due to glucocorticoids: try to ↓ dose and use steroid-sparing drugs.
- Incidental pituitary lesions can be seen on scans in ~10% of the population and are not pathological.
- Treat HT and DM.
- Testing and definitive treatment should be done at a specialist centre.

Renovascular hypertension

- Renal artery stenosis caused by atherosclerotic disease (85%) or fibromuscular dysplasia (15%).
- Other causes for ↑ renin and aldosterone: renal infarction, volume depletion, diuretics, cardiac or hepatic failure. Rarely overproduction of renin from a juxta-glomerular tumour.

Presentation

- Should be considered in patients with vascular disease and ↓ renal function following an ACE inhibitor.
- May have a renal artery bruit, and signs of peripheral vascular disease, hypertensive retinopathy, renal damage, severe HT, flash pulmonary oedema.

Diagnosis

↑ peripheral plasma renin activity and ↑ plasma aldosterone.

Management

Referral to a specialist centre is advised.

Gynaecomastia

Gynaecomastia is ↑ amount of tissue of the male breast, usually because of an endocrine disorder. Usually from ↑ oestrogen/androgen ratio and may → distress.

Causes

Normal after puberty, or in neonatal period or in the elderly. Can be caused by commonly prescribed drugs:

- Oestrogens, GH, anabolic steroids, cyproterone.
- Antimicrobials: isoniazid, ketoconazole, metronidazole, efavirenz.
- Cimetidine, omeprazole.
- Digoxin, methyldopa, spironolactone.
- Haloperidol, phenothiazines, tricyclic antidepressants, alcohol, cannabis.

Endocrine causes:

- Hypogonadism.
- Hyperprolactinaemia.
- Liver cirrhosis.

Presentation

- Breast or nipple pain.
- Progressively enlarging breasts.

Diagnosis

- Try to distinguish between true gynaecomastia and obesity.
- Examination of the testes may reveal a testicular tumour.
- If gynaecomastia long-standing since puberty, and drugs excluded, it is probably benign.
- Screen for liver and renal abnormalities, hCG levels, luteinizing hormone, testosterone, and oestradiol.

Management

If the cause is unclear, refer to a specialist centre.

Hypoadrenalism

May be 1° (Addison's disease) or 2°, e.g. from pituitary disease.

Causes of primary hypoadrenalism

- Autoimmune (sometimes occurs with T1DM, coeliac disease, vitiligo hypoparathyroidism, and hypothyroidism) and TB.
- Less common: adrenoleukodystrophy, metastases, HIV related, or idiopathic.

Causes of secondary hypoadrenalism

Post pituitary surgery or cranial irradiation, pituitary adenoma, trauma, craniopharyngioma.

Presentation

- In 1° hypoadrenalism, hyperpigmentation of the buccal mucosa and palmar creases (in Africa such pigmentation is non-specific).
- Other common symptoms: postural hypotension, collapse, abdominal pain, weakness, diarrhoea, lower back pain, weight loss, fatigue, dizziness, cramps, headaches, depression, craving salt.

Diagnosis

- Hypoglycaemia, eosinophilia, hypercalcaemia, anaemia, neutropenia, lymphocytosis.
- Hyponatraemia, hyperkalaemia, metabolic acidosis.
- During an acute illness a plasma cortisol <250nmol/L is diagnostic, and level <400nmol/L is suggestive of hypoadrenalism.
- 1° hypoadrenalism has ↑ ACTH with ↓ cortisol.
- 2° hypoadrenalism has low/normal ACTH with ↓ cortisol.
- Consider hypoadrenalism if plasma cortisol <400nmol/L between 8am and 9am.
- Short ACTH stimulation test (Synacthen test): cortisol >500nmol/L after ACTH dose excludes hypoadrenalism.

Management

- Replace hydrocortisone 10mg in the morning, 5mg at lunchtime, and 5mg at 4pm.
- Fludrocortisone is to correct ↑ potassium and ↓ sodium in 1° hypoadrenalism, not usually required in 2° hypoadrenalism. Starting dose of fludrocortisone 50 micrograms daily, adjusted according to BP and electrolytes.
- Refer to a specialist.

Adrenal crisis

This is a medical emergency that may be precipitated by infection, surgery, or trauma.

Presentation

- Hypotension/collapse.
- Loss of consciousness.
- Hypoglycaemia/hyponatraemia.
- Convulsions/fever.

Management

- Give 100mg IV hydrocortisone 8hrly, and fluids if dehydrated.
- Patients should never stop steroids and if vomiting prevents intake, attend an emergency centre.
- Double the dose of hydrocortisone for stress, dentistry, and fevers.
- Wear a bracelet or necklace identifying steroid use.

Hypercalcaemia

General points

- Need to correct serum calcium value for the serum albumin.
- Relatively common.

Causes

1° hyperparathyroidism and malignancy (e.g. myeloma) account for >90% of cases.

Don't forget

- Drugs especially thiazide diuretics.
- 3° hyperparathyroidism.
- Granulomatous diseases, e.g. TB/sarcoidosis.

Clinical features

- Mild hypercalcaemia (calcium <3mmol/L often asymptomatic or non-specific symptoms, e.g. constipation, fatigue, depression).
- Serum calcium 3–3.5mmol/L often well tolerated long term.
- Serum calcium >3.5mmol/L or acutely >3mmol/L may → marked symptoms, e.g. polyuria, dehydration, anorexia, nausea, muscle weakness, and confusion/coma.

Diagnosis

Check calcium, phosphate, Cr, PTH.

Management

- Identify and treat cause—including drugs.
- Mildly asymptomatic/suspect hyperparathyroidism: refer for assessment.
- Severely symptomatic: rehydrate with normal saline 4–6L/24h. Give furosemide 40mg/L once rehydrated—serum calcium may drop by 0.5–0.8mmol/L if dehydration is very severe. May need to refer for IV bisphosphonates.

If mild and/or suspected hyperparathyroidism, encourage ↑ fluid intake, avoid thiazides, refer to consider parathyroidectomy.

Hypocalcaemia

General points

- Relatively common.
- Ranges from asymptomatic in mild cases to life-threatening in severe/acute hypocalcaemia.

Causes

Mostly due to:

- Hypoparathyroidism.
- Vitamin D deficiency.

Don't forget

- Renal failure.
- Hypomagnesaemia.

Clinical features

- Numbness/tingling fingertips, toes, around mouth.
- Cramps/tetany.
- May have no clinical signs if mild.
- Carpopedal spasm when BP cuff inflated > systolic BP for 3min (Trousseau's sign).
- Twitching of facial muscles if facial nerve tapped (Chvostek's sign).
- Arrythmias (ECG may show long QT).
- Check neck for scar of thyroid surgery.

Diagnosis

Check serum total calcium, albumin, magnesium; phosphate, Cr, alkaline phosphate, PTH.

Management

Identify underlying cause.

If severe/acute

- Give 10–20mL 10% calcium gluconate diluted in 50–100mL of normal saline infused over 10min. (Calcium chloride often → local irritation.)
- Repeat until symptoms have cleared.
- If persistent hypocalcaemia, administer calcium gluconate IV at 0.5–2.0mg/kg/h over longer periods; aim to raise serum calcium into low normal range and maintain.
- Start oral calcium and vitamin D supplementation.

If mild/chronic

- Keep serum calcium in low normal range.
- Long-term therapy oral calcium supplements: 1–3g of elemental calcium in 3–4 divided doses with meals to ensure optimal absorption.
- Add vitamin D.
- Monitor for hypercalcaemia.

Hyperkalaemia

General points

- Defined as K^+ >5.5mmo/L (exclude blood sample haemolysis as cause).
- Absence of symptoms does not exclude severe hyperkalaemia.
- Immediate danger is cardiac effect.
- Assess need for urgent intervention.

Causes

- AKI/chronic renal failure.
- ACE inhibitors.
- Angiotensin receptor blockers.
- Potassium-sparing diuretics, e.g. spironolactone.
- Addison's disease.
- Haemolysis.

Clinical features

- Often asymptomatic.
- Severe—muscle weakness, ascending paralysis, palpitations.

Diagnosis

If patient at risk of hyperkalaemia and K^+ result not available, check ECG (peaked T wave, i.e. T wave as tall as the R wave indicative of hyperkalaemia).

- Check Cr, glucose, urea, acid base.
- May need to measure renin, aldosterone, cortisol, ACTH.

Management

- Check for underlying cause/remove culprit.
- Assess need for urgent intervention:
  - In life-threatening hyperkalaemia (K^+ >7.0mmol/L, ECG changes) give 10mL 10% calcium gluconate by slow IV to prevent arrhythmia.
- Give 10U of rapid-acting insulin and 50mL 50% glucose IV. If DM with blood glucose >15mmol/L, then IV glucose not needed.
- Salbutamol inhalation.
- Increase K^+ losses: Sodium polystyrene sulfonate 15–30g 8hrly × 3 doses and reassess K^+.

Chronic

Sodium polystyrene sulfonate 15mg up to three times a day.

Hypokalaemia

General points

- Defined as K^+ <3.5mmol/L.

Causes

Most common causes arise from:

- ↓ intake: e.g. eating disorders.
- ↑ loss: diuretics or other causes of polyuria, vomiting, and diarrhoea.
- Intracellular shift: salbutamol, insulin.

Clinical features

- Usually asymptomatic, but K^+ <2.5mmol/L may → muscle weakness.
- Very low K^+ can → arrhythmia.

Diagnosis

If cause not clinically apparent, test urine K^+:

- Urine K^+ <20mEq/L = GI tract loss, poor intake, or intracellular shift.
- Urine K^+ >20mEq/L = renal loss. Consider hypomagnesaemia, 1° or 2° hyperaldosteronism, ↑ cortisol, and renal tubular defects.

Treatment

- Treat underlying cause.
- Adult daily K^+ requirement is ~60mmol/24h.
- Additional K^+ needed if hypokalaemia or ongoing losses.
- Oral supplements (40–60mmol/d) or fresh fruit, vegetables.
- If hyperaldosteronism, give spironolactone 100–400mg/d (25–50mg/d in heart failure).

Hyponatraemia

General points

- Defined as Na^+ <135mmol/L.

Clinical features

- Asymptomatic.
- Mild: headache, lethargy, dizziness.
- Severe: confusion, ataxia, seizures, coma, respiratory depression.

Diagnosis

- Measure serum Na^+, urea, glucose.
- Calculate the serum osmolality [2 × Na^+ (mmol/L) + urea + glucose (mmol/L)].
- Measure urinary Na^+.
- Use the serum osmolality, urine Na^+, and hydration status to determine the likely cause (Box 11.2).
- Before making a diagnosis of SIADH exclude hypothyroidism and hypoadrenalism.

Treatment

- Use the following formula to determine the change in serum sodium using 1L of any infusate:
  - Change in serum Na^+ = infusate Na^+ − serum Na^+/total body water (TBW) + 1.
    - TBW in non-elderly man = 0.6 × body weight (kg).
    - TBW in non-elderly woman = 0.5 × body weight (kg).
    - TBW in elderly man = 0.5 × body weight (kg).
    - TBW in elderly woman = 0.45 × body weight (kg).
- Acute (48h) or severe hyponatraemia:
  - Use 3% saline.
  - Aim to ↑ serum Na^+ by 2mmol/L/h.
  - Check the serum Na^+ every 2h.
  - Stop when symptoms improve.
  - Mild symptoms or asymptomatic or chronic (>48h):
    - Treat the underlying cause.
    - Aim to ↑ Na^+ level <8mmol/L in the 1st 24h to avoid causing central pontine myelinolysis (quadriplegia, abnormal eye movements).

Hypernatraemia

General points

- Defined as Na^+ >145mmol/L.

Clinical features

- Asymptomatic.
- Flushed skin, fever, agitation, anxiety, restless, confusion.
- Elevated BP, oedema, dry mouth, dehydration.

Diagnosis

- Measure serum and urine Na^+, urine osmolality.
- Use the urine osmolality, urine Na^+, and hydration status to determine the likely cause (Box 11.3).

Treatment

- Treat the underlying cause.
- Usually require rehydration with either saline (0.45% or 0.9%) or free water.

Box 11.2 Causes of hypernatraemia

- Hypovolaemic:
  - Urinary Na^+ <20mmol/L—extrarenal losses (↑ sweating, burns, diarrhoea, fistulas).
  - Urinary Na^+ >20mmol/L—renal losses (diuretics), post-obstruction, renal disease.
- Euvolaemic:
  - Renal losses (diabetes insipidus, hypodipsia) (urine osmolality usually <300mOsm/kg).
  - Extrarenal losses (urine osmolality usually >800mOsm/kg).
- Hypervolaemic:
  - Hyperaldosteronism, Cushing's syndrome, excess salt intake.

Ophthalmology

David Yorston

Global blindness

WHO estimates that 36 million people worldwide are blind (acuity <3/60 in the best eye); 90% of them live in resource-poor countries, and 80% are aged >50yrs. The number of blind people ↑ every year with ↑ ageing of the world population. Recent efforts to improve eye care, and to treat cataract and refractive error, have ↓ global blindness. Another 217 million people have visual impairment (acuity >3/60 but <6/18).

Five diseases (cataract, trachoma, onchocerciasis, vitamin A deficiency, and refractive errors) are all avoidable (preventable or curable) and cause >70% of visual impairment worldwide.

- Cataract is the commonest cause of blindness, with ~12.6 million blind by cataracts. In 2008, ~15 million cataract operations were performed worldwide; cataract surgery in previously visually impaired individuals can alleviate a household's poverty.
- Trachoma and onchocerciasis are responsible for ~5% of all blindness. Both occur in poor communities. Blindness can be prevented through relatively simple treatment.
- Vitamin A deficiency is major cause of blindness in children in poor communities.
- With improvements in hygiene and 1° healthcare → ↑ life expectancy, esp. in Asia, degenerative conditions (e.g. glaucoma, diabetic retinopathy, and age-related macular degeneration) are the fastest growing causes of blindness.
- Uncorrected refractive error, especially myopia, is the leading cause of visual impairment, esp. in Asia. For people living in isolated communities, eye tests and spectacles are often unavailable or unaffordable.

Presenting features of eye disease

Main symptom

- *Visual loss*: cannot see in the distance with one or both eyes. Onset may be rapid or gradual.
- *Red painful eye(s)*: eye pain or discomfort, sometimes with a history of trauma.
- *Inability to read*: ↓ near vision, despite good distance vision. Due to presbyopia >40yrs.
- *Other symptoms*: include watering eyes, flashing lights.

Examination

- Measure visual acuity (VA) with and without pinhole (Box 12.1).
- Examine the cornea and pupil (Box 12.2) with a torch-light.
- After dilating pupil, examine optic disc and retina with ophthalmoscope.

Box 12.1 Testing visual acuity

All eye patients must have their VA measured. Any opacity of lens or cornea, or damage to central retina or optic nerve, → ↓ VA. Only distance acuity is measured at 6m; near vision will always be ↓ in older patients who do not have reading glasses. Each eye is tested individually, using patient's own distance glasses, if they have any.

Patient stands 6m from chart and covers one eye. Literate patients read out letters, starting at top. Illiterate patients use an 'E' chart, indicating if it is pointing left or right, up or down.

Each line on chart is labelled with a number. Top line is 60, second is 36, etc. Numbers indicate distance at which that line can be read by a normal eye. Third line on chart can normally be read at 24m, so if a patient can only read this line at 6m, the VA is 6/24. Normal vision is 6/6. People can do most normal daily activities with a VA of 6/18.

If patients cannot see top line at 6m, bring them closer. If they can read it at 3m, acuity is 3/60. If they cannot see top line, ask them to count your fingers, see your hand move, or see light. If they have no perception of light, it is probable that eye is permanently blind and no treatment will restore vision.

Sometimes the VA is ↓ because the patient needs glasses. You can partially overcome a refractive error by using a pinhole: take some dark card and with a hot 21G needle, make a hole in the centre. The patient looks through the hole; if vision improves, the eye has a refractive error.

Box 12.2 Pupil examination

- Seat the patient in a dimly lit room, focused on distant object.
- Use a bright light and test each pupil reaction in turn. Examine reaction of both pupils when one pupil is illuminated.
- Check accommodation response by asking patient to focus on your finger held ~10cm in front of their nose. If the patient accommodates, eyes will converge and pupils constrict.
- Observing movement of a darkly pigmented iris against a black pupil in a dim room is difficult. Your examination will be more reliable with magnification.

Visual loss: refractive errors

Usually present with gradual ↓ vision (Table 12.1). Four types of refractive errors:

Myopia

Short-sightedness, → poor distance vision, but good near vision. Myopia can be diagnosed as follows:

- Distance vision improves with a pinhole.
- Near vision is good, despite poor distance vision.

Myopia can be corrected with –ve (concave) lenses. In absence of trained refractionist, the following method will usually give an acceptable spectacle correction. If you have trial lenses available, test one eye at a time. Start with –1 lens and gradually ↑ strength by steps of –1, measuring VA with every lens. When ↑ power does not → further improvement, choose minimum power that will give best visual acuity. Repeat process for the other eye.

Hypermetropia

Long-sightedness, → difficulty with near vision in young people. Hypermetropia uncommon <40yrs, but can be corrected with +ve (convex) lenses.

Aphakia

Severe hypermetropia due to removal of the lens. Aphakia is becoming less common as most cataract operations include insertion of an intraocular lens. Can be corrected with a +11.0 dioptre lens.

Astigmatism

Different refraction in horizontal and vertical axes of the eye. Can be corrected with cylindrical lenses.

Presbyopia

Poor accommodation → difficulty with reading and near vision >40yrs. Can be corrected with reading spectacles that usually have (+ve) strength of between +1.00 and +4.00 dioptres. In patients <50yrs, +1 to +2 is sufficient. Patients >70yrs will require +3 to +4.

Table 12.1 Common causes of poor distance vision

	Causes	Signs and symptoms	Management
Refractive error	Myopia Hypermetropia (Aphakia)Astigmatism Presbyopia	Vision ↑ with pinhole	Spectacles
Cataract	Usually age related Also: Eye injuries Diabetes iritis	White or grey pupil Pupil reacts to light Absent or ↓ red reflex	Cataract removal if VA is <6/18, or if lifestyle affected
Corneal opacity	Corneal ulcer Trachoma Vitamin A deficiency Leprosy	White scarring of the cornea in a quiet white eye Pupil difficult to see Absent or ↓ red reflex	Often no treatment Surgery may be considered when both eyes affected
Diseases of optic nerve and retina	Glaucoma Optic atrophy Macular degeneration Diabetic retinopathy Hypertensive retinopathy Retinal detachment	Cornea and lens should be clear Pupil may not react normally to light Specific signs seen with an ophthalmoscope in retina or optic nerve	Management directed at cause

Cataract

Cataracts → gradual, progressive, and painless ↓ VA. Because they progress very slowly, most patients who are blind from cataract never come to an eye clinic, since they accept their blindness as normal for their age. Elimination of cataract blindness requires community involvement to change attitudes and ↓ barriers that block access to eye services. Cataract surgery → significant impact on poverty. Even one family member with moderate cataract → significantly ↓ household income, but income recovers if the affected person has a cataract operation.

Diagnosis

When complete, cataracts can be seen as a white opacity in the pupil, while younger cataracts give a grey-white appearance to the pupil. Examination with an ophthalmoscope, after dilation of the pupil, shows opacity in the red reflex with poor fundus detail due to lens opacity (Box 12.3). The pupil reaction to light is normal in an uncomplicated cataract.

Management

There is currently no way to prevent cataracts forming. The only treatment is surgery to remove the lens and replace it with an artificial intraocular lens. Surgery is usually performed under local anaesthesia. Following surgery, 80–90% of eyes should be able to see 6/18 or better. The patient may then need corrective spectacles to obtain optimal vision.

Box 12.3 Lens examination

When studying the lens or other anterior eye structures: set your ophthalmoscope to its strongest +ve lens (typically +10 to +30). This allows instrument to focus a few centimetres away. Test by examining your own finger-tip to check distance of focus. By moving in and out you can see cornea, iris, anterior chamber, and lens in fairly good detail. This is a low-tech way to inspect eye with good illumination and high magnification.

Corneal opacity

Diagnosis

White opacity on the cornea, which usually prevents clear view of iris and pupil. May follow corneal ulcer, or injury, or it may be caused by trachoma, vitamin A deficiency, or leprosy. Most corneal scars are preventable with, e.g. vitamin A supplements or by good management of the original condition, e.g. corneal ulcer.

Management

If both eyes have severe visual loss, then a corneal graft or optical iridectomy may improve vision. Specialist care and good follow-up are essential.

Glaucoma

Most glaucoma is chronic, with gradually progressive ↓ peripheral vision due to optic nerve damage. There are no symptoms until VA ↓, which occurs only after most of the optic nerve has been destroyed.

Acute glaucoma is uncommon, and presents with a red painful eye (➲ Acute glaucoma, p. 529).

Diagnosis

Chronic glaucoma difficult to diagnose. Detecting peripheral visual field loss requires complex equipment. Measuring intraocular pressure (IOP) is simpler, but unreliable, as many patients with ↑ IOP do not have glaucoma. Some patients with glaucoma have normal IOP. More reliable diagnosis is by observing ↑ size of the optic cup; this requires expertise.

Management

Reduce IOP with filtration surgery or lifelong eye drops (e.g. timolol 0.25% bd). Treatment prevents progression and preserves sight, but does not improve vision, so patients who are already blind need not be treated.

Macular degeneration

As more people survive into old age, macular degeneration ↑ as a cause of blindness. Atrophic (dry) macular degeneration is the commonest type. It → gradual, often bilateral ↓ vision in people >70yrs old. Ophthalmoscopy shows atrophy of the central retina. Because it is slowly progressive, it usually → ↓ VA rather than blindness. At present it is untreatable.

Exudative (wet) macular degeneration is caused by abnormal new blood vessels that grow out from the choroid under the macula. This usually occurs quite rapidly over a few weeks. The blood vessels leak fluid and bleed. Eventually they are replaced by scar tissue, and the central vision is destroyed. This condition is treatable if detected at an early stage (vision 1/60 or better). Patients with recent onset of symptoms, and vision of 1/60 or better, associated with exudates or haemorrhage at the macula should be referred to an eye specialist. Treatment consists of monthly injections of anti-vascular endothelial growth factor drugs into the vitreous cavity.

Diabetic retinopathy

The prevalence of diabetes ↑ globally. ~40% of diabetic patients will have some retinopathy; in ~5% it is sufficiently severe to threaten vision. As well as retinopathy, people with diabetes also have an ↑ risk of cataract.

Retinopathy is caused by damage to the capillaries in the retina. Capillaries may leak, → oedema and exudates, or they may become blocked, → to ischaemia.

Commonest cause of visual loss in diabetic retinopathy is *maculopathy*, where macular region of retina (provides central vision) is affected by retinopathy. Oedema is difficult to detect with ophthalmoscope, but hard exudates (lipid deposits in the retina) are easier to see.

Occlusion of retinal capillaries → ischaemia and hypoxia → growth of new vessels from surface of retina on posterior vitreous face (proliferative retinopathy). These vessels may bleed, → vitreous haemorrhage, or contract, → traction detachment of the retina.

Diagnosis

In order to detect retinopathy at an early and easily treatable stage, all diabetics should have an annual eye examination, including measurement of VA, and a dilated fundus exam. International classification of diabetic retinopathy defines the different stages and guides referral to an ophthalmologist (Table 12.2).

Treatment

- Laser treatment → ↓ new vessels in proliferative retinopathy → ↓ risk of loss of vision in maculopathy. It cannot restore sight that has been lost.
- Anti-vascular endothelial growth factor injections—monthly injections of these drugs into the vitreous may improve vision in eyes with maculopathy. They are more effective than laser treatment, but must be given regularly for years.

Table 12.2 International classification of diabetic retinopathy

	Definition	Action
Retinopathy grading		
None	No retinopathy	Re-examine in 12mths
Mild non-proliferative	Microaneurysms only	Re-examine in 12mths
Moderate non-proliferative	More than mild, but less than severe	Re-examine in 6–12mths
Severe non-proliferative	>20 intraretinal haemorrhages in all 4 quadrants. Definite venous beading in >2 quadrants. Intraretinal microangiopathy in >1 quadrant	Refer to ophthalmologist May need laser treatment
Proliferative	Visible new vessels; vitreous haemorrhage; traction detachment	Refer for urgent laser treatment
Maculopathy grading: macular oedema		
Absent	No exudates or oedema	Re-examine in 12mths
Mild	Exudates in posterior pole, but distant from fovea	Re-examine in 6–12mths
Moderate	Exudates in posterior pole close to fovea	Refer to ophthalmologist
Severe	Exudates in posterior pole involving fovea	Refer to ophthalmologist

Red eye

History and examination

- Ask about any known cause, especially injury.
- Measure the VA.
- Carefully examine eyelids, conjunctiva, cornea, and pupil with a bright torch. Examination will be more reliable if you also use magnification.

Injuries to the eye

Ask about any injury to or foreign body into the eye.

Corneal or conjunctival foreign bodies (FBs)

The history is usually straightforward. The FB may be obvious or you may need to evert the upper eyelid to check the conjunctiva for objects scratching the cornea each time the patient blinks.

To remove the FB

- Lie the patient flat.
- Apply local anaesthetic drops, e.g. lidocaine 4% to the conjunctiva.
- Light the eye with a torch so that the FB is easily visible.
- Loupe magnification is useful.
- Lift off the FB carefully with a sterile needle, or cotton bud.
- Give an antibiotic eye ointment or drops and eye pad for 1d.

Corneal abrasion

Trauma removes some corneal epithelium → sudden severe pain and photophobia. To confirm the diagnosis, apply fluorescein which stains the cornea lacking epithelium. Treat with an antibiotic eye ointment or drops until the pain has gone and the epithelium is healed, typically in ~24–48h.

Hyphaema

Severe blunt injury (e.g. hit in eye by stone/fist) may → bleeding in the eye. A blood level (hyphaema) may be visible between cornea and iris. This will usually resolve over a few days with rest. Avoid aspirin, as this may → further bleeding. If the eye is painful, give acetazolamide 250mg qds for 3–7d to ↓ IOP and topical prednisolone 0.5–1.0% drops qds to ↓ inflammation. If the hyphaema has not resolved after 5d, consult an eye specialist.

Penetrating eye injury

A penetrating injury (involving the full thickness of cornea or sclera) is serious. Common causes incl. thorns, or splinters when chopping firewood. Be very careful examining the eye as pressure may aggravate the injury. Gently apply an antibiotic eye drop (not ointment), put an eye pad over the eye, and refer the patient to a specialist immediately. Systemic antibiotics (ciprofloxacin 750mg bd) may ↓ risk of intraocular infection. If immediate referral is not possible, then conservative treatment with antibiotics and an eye pad is probably better than a non-eye surgeon 'having a go'.

Red eye with no injury

If there is no history of eye injury, consider:
- Conjunctivitis.
- Corneal ulcer.
- Iritis.
- Acute glaucoma.

See Table 12.3.

Table 12.3 Common causes of non-traumatic acute red eye

	Acute glaucoma	Iritis	Corneal ulcer	Conjunctivitis
Pain	Severe	Moderate	Moderate to severe	Irritation
Visual loss	Severe	Variable	Variable	None
Redness	Around corneal limbus	Around cornea	Around cornea	Especially in fornices
Cornea	Oedematous and hazy	Keratic precipitates seen with magnification	Opacity on cornea	Normal
Pupil	Half dilated and fixed	Constricted and irregular	Normal	Normal
Special features	↑ IOP	Irregular pupil may be more obvious as the pupil is dilated	Stains with fluorescein	Discharge, often bilateral
Treatment	Acetazolamide 250mg qds to ↓ IOP Surgery usually needed	Dilate pupil and give topical steroids if certain of diagnosis	Topical antimicrobials	Topical antibiotics

Conjunctivitis

Infective conjunctivitis

Infection or inflammation of the conjunctiva is common in the tropics. Important causes are given in Table 12.4.

Diagnosis Irritation of the eye with discomfort, but normal vision. Eye is red with ↑ discharge. Severe disease may → swelling of eyelids (chemosis).

Management Give an antibiotic eye ointment or drops, e.g. chloramphenicol 0.5–1%, initially 2hrly, then qds for 5–7d. Do not pad eye.

Ophthalmia neonatorum

Conjunctivitis in the first 4wks of life, usually due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis* (➲ Antibiotic therapy of infections in young infants, p. 21). The lids are very swollen and covered with pus. Untreated, gonococcal infection rapidly → complete destruction of the cornea and permanent blindness.

Management

Give appropriate systemic and topical antibiotics which will be effective against local strains of gonorrhoea (➲ Gonorrhoea, p. 670). Most cases of ophthalmia neonatorum may be prevented by irrigating eyes of all newborn babies with 2.5% povidone-iodine solution: one drop in each eye immediately after delivery, repeated once within first postnatal day.

Chlamydial conjunctivitis (trachoma)

See ➲ Trachoma, p. 530.

Epidemic haemorrhagic conjunctivitis

Highly contagious viral conjunctivitis usually due to enteroviruses. After 1–2d incubation period, multiple petechial haemorrhages occur. Most patients recover quickly.

Management Give an antimicrobial agent, e.g. povidone-iodine 1.25% 1 eye drop qds, to help ↓ transmission and reassure the patient.

Allergic conjunctivitis

Children and young adults may develop chronic allergic conjunctivitis (vernal conjunctivitis). Severe itching/irritation with a mucus discharge, sometimes with swelling and pigmentation around the cornea.

Management

Treatment with topical steroids is effective, but has serious side effects. If possible, children with severe disease should be seen and treated by an eye specialist. In milder cases, parents should be reassured that the condition does not lead to loss of sight and is usually self-limiting—children 'grow out of it'. Symptoms may be improved by bathing eyes with cold clean water.

Table 12.4 Common causes of conjunctivitis

Cause	Age	Secretions	Special features	Treatment
Bacterial	Any	Purulent	Red and swollen; purulent discharge	Topical antibiotics for 5d
Ophthalmia neonatorum	First 4wks of life	Purulent	Very red and swollen; purulent discharge	Systemic and topical antibiotics for 10d
Viral	Any	Watery	May have corneal lesions	Symptomatic only
Chlamydial (trachoma)	Usually young children	Muco purulent	Follicles and papillae on upper lid	Azithromycin 1g orally or tetracycline ointment for 6wks
Allergic (vernal)	Children	Stringy mucus	Very itchy, large papillae; infiltrate and pigmentation around cornea	Cromoglicate and possibly steroid eye drops for symptoms

Box 12.4 Orbital and periorbital cellulitis

Vital to determine whether the cellulitis just involves the eyelids (periorbital or periocular) or whether the eye itself is involved (orbital cellulitis).

- *Orbital cellulitis*: an emergency → blindness and severe complications (including abscess formation, cavernous sinus thrombosis, optic nerve damage, meningitis, and death). More common in children than in adults.
- *Periorbital (periocular) cellulitis*: may occur from local superficial infection, spread from sinus infection, or from bacteraemia (previously commonly *Haemophilus influenzae* type b (Hib) in young children, but incidence ↓↓ due to Hib immunization). Common pathogens are *Staphylococcus aureus*, streptococci, and non-typeable *H. influenzae*. In sinus-associated infection, may involve Gram –ve and anaerobic bacteria. Fungal infection is rare, and more likely to occur with immune deficiencies.

Clinical features

Both types have periorbital erythema and tenderness. Orbital cellulitis is suggested by ophthalmoplegia, proptosis, ↓ VA, chemosis, or signs of systemic toxicity.

Management

Antibiotics, e.g. ceftriaxone 2g IV od (children 50mg/kg IV od) plus metronidazole 400mg tds oral (child 1mth–12yrs 7.5mg/kg tds; max. 400mg tds). Oral antibiotics might be considered for mild periorbital cellulitis in a clinically well patient. If available, consider CT head to look for sinus infection or complications, e.g. abscess formation. Seek ENT and ophthalmology review.

Corneal ulcers

May occur spontaneously or follow corneal abrasion. There are many causes (Table 12.5).

Diagnosis

Usually severe pain, watery discharge, and blurred vision; redness around cornea, which is cloudy, often with localized white or grey opacity, which stains with fluorescein. In severe cases, there may be a fluid level of pus inside eye ('hypopyon'). Bacterial or fungal aetiology may be identified by Gram stain and culture of a scraping from edge of ulcer—this should only be done in an eye clinic.

Management Depends on the cause (Table 12.5).

Snake venom ophthalmia

Spitting cobras (elapids) have evolved fangs that eject a spray of intensely irritant venom into eyes of an aggressor, → intense pain, conjunctivitis, corneal erosions (and occasionally anterior uveitis). 2° bacterial infection of corneal erosions may → permanent scarring and blindness.

Management Wash venom from affected eye or mucous membranes with large amounts of water. Apply topical chloramphenicol or tetracycline ointment. 0.1% adrenaline eye drops relieve the pain.

Table 12.5 Common causes of corneal ulceration

Cause	Predisposing factors	Clinical features	Treatment
Herpes simplex	Fever	Irregular branching ulcer	Ganciclovir ointment 5× daily for 2wks
Bacteria	Trauma	Often severe pain and ↓ VA; +/– hypopyon	Topical and/or subconjunctival antibiotics (e.g. ciprofloxacin, ofloxacin, cefuroxime, or gentamicin) hourly for 48h then qds for 5d or until epithelium healed
Fungus	Hot, humid areas, minor trauma	Often severe pain and ↓ VA; +/– hypopyon	Antifungals, e.g. natamycin 5% eye drops hourly for ≥2wks
Vitamin A deficiency	Measles Malnutrition Mala bsorption	Dry cornea. Central 'punched out' oval ulcer, often in a quiet eye	Vitamin A 200,000IU start, then after 1d and 2wks
Exposure	Leprosy Facial burns	Eyelids do not close; lower third oval ulcer	Antibiotic ointment Tape eye closed Tarsorrhaphy

Uveitis

Inflammation of the uvea may involve both anterior uvea (iris and ciliary body) and posterior uvea (choroid). Causes incl. infections (e.g. leprosy, onchocerciasis, toxoplasmosis, TB, syphilis) and systemic diseases (e.g. certain types of arthritis, sarcoidosis, Behçet's disease, inflammatory bowel disease). However, most cases, esp. of anterior uveitis, have no known cause, and multiple investigations are unnecessary.

Anterior uveitis (iritis, iridocyclitis)

Clinical features Pain of iritis varies from mild to severe and → photophobia +/− blurring of vision. Blood vessels around margin of cornea (limbus) are dilated. Iris constricts and adheres to front of lens (posterior synechia), making pupil irregular. These synechiae can → 2° glaucoma and cataract. When pupil is dilated, adhesions may break, leaving iris pigment on front of lens. Pus collecting in anterior chamber can be seen with magnification (slit lamp).

Management Dilate pupil to break any posterior synechiae (cyclopentolate 1% or atropine 1% 2–3×/d for 2wks); give anti-inflammatory agents to ↓ inflammation (prednisolone 0.5–1.0% drops hourly initially, then gradually ↓ over 4wks).

Posterior uveitis

Clinical features Presents with ↓ VA because of involvement of retina and vitreous. Not usually painful, but severe attack may → discomfort. A white inflammatory lesion may be seen in retina. Once inflammation has settled, characteristic scars occur with pigment atrophy and hypertrophy.

Management Requires treatment of cause.

Acute glaucoma

If the IOP ↑ suddenly over a few hours, eye becomes red and very painful with severe loss of vision. Acute glaucoma is unusual in people <50yrs. May occur spontaneously or as a complication of a completely white cataract. Cornea appears hazy and pupil is semi-dilated and does not react to light. IOP is very high, which can → N&V. Acute glaucoma may be misleading and can present as a sudden severe headache, or mimic an acute abdomen.

Management Give acetazolamide 500mg stat oral and then 250mg qds oral. Refer to eye specialist, since urgent surgery is usually required.

Trachoma

Trachoma is a chronic conjunctivitis caused by infection with *Chlamydia trachomatis*, serotypes A, B, and C. Active infection → scarring of the upper conjunctiva and tarsal plate → the eyelashes turn in and scratch the cornea → ulceration, scarring, and blindness (➲ Colour plate 25a–e).

Transmission

Trachoma occurs mainly in dry areas, with inadequate water and sanitation. The classic environment can be described as:

- *Dry*: lack of water.
- *Dirty*: lack of sanitation.
- *Discharge*: lack of personal hygiene.

Transmission from child to child, and child to mother occurs through:

- *Flies*: flies go from individual to individual.
- *Fingers*: direct contact with ocular discharge.
- *Family*: within the family, child to child.

Clinical features and diagnosis

See the 5-point WHO grading system in Box 12.5. TF and TI are found mainly in pre-school children; TS, TTr, and CO occur more commonly in women than men, starting at ~15yrs and gradually ↑ in prevalence.

How to examine the eye for trachoma

Use good light (sunlight or strong torch) and 2–2.5× magnification. Examine each eye separately.

Look for trichiasis (either in-turned lashes or previously removed eyelashes). Push upper lid upwards slightly to expose lid margins.

Check cornea for opacities

Check inside upper eyelid by everting it. Ask patient to look down; gently take hold of eyelashes between thumb and first finger of left hand, and evert upper eyelid using a glass rod or similar instrument in right hand. Steady everted lid with left thumb and examine conjunctiva for follicles, intense inflammation, and scarring.

Management

Azithromycin 1g oral as single dose (20mg/kg if <45kg) or tetracycline 1% topical ointment both eyes bd for 6wks. Azithromycin treatment of all children in the community ↓ transmission in adults as well.

Where mass distribution of azithromycin has been used, it has been associated with ↓ child mortality. Entropion and trichiasis will require surgery. Although surgery is initially successful, entropion will recur in up to 40% of patients.

Prevention

The acronym 'SAFE' summarizes the strategies for prevention (Box 12.6). Control requires first identifying a community with blinding disease. This can be done using the grading scheme and a survey of children of 1–10yrs for TF and TI, and women over >15yrs for TT. A prevalence of TF in >20%, or TT >1%, identifies a community with severe disease. WHO recommends three rounds of mass drug administration with azithromycin in districts where the prevalence of TF is ≥10% in children aged 1–9yrs.

Box 12.5 Trachoma grading

See ➲ Colour plate 25. Signs must be obvious to be considered present. Grading is important to decide whether mass treatment is warranted.

- *Normal*: normal conjunctiva is pink, smooth, thin, and transparent. Over whole area of tarsal conjunctiva, there are normally large deep-lying blood vessels that run vertically. Dotted line in ➲ Colour plate 25a shows the area to be examined.
- *Trachomatous inflammation—follicular (TF)*: the presence of >5 follicles in the upper tarsal conjunctiva. Follicles are round swellings, paler than the surrounding conjunctiva, appearing white, grey, or yellow. Follicles must be >0.5mm in diameter (➲ Colour plate 25b).
- *Trachomatous inflammation—intense (TI)*: pronounced inflammatory thickening of the tarsal conjunctiva that obscures >50% of the normal deep tarsal vessels. The conjunctiva appears red, rough, and thickened. There are numerous follicles, which may be partially or totally covered by the thickened conjunctiva (➲ Colour plate 25c).
- *Trachomatous scarring (TS)*: scars are easily visible as white lines, bands, or sheets in the tarsal conjunctiva. They are glistening and fibrous in appearance. scarring, especially diffuse fibrosis, may obscure the tarsal blood vessels (➲ Colour plate 25d).
- *Trachomatous trichiasis (TTr)*: eyelash rubs on the eyeball. Evidence of recent removal of in-turned eyelashes should also be graded as trichiasis (➲ Colour plate 25e).
- *Corneal opacity (CO)*: easily visible corneal opacity over the pupil. The pupil margin is blurred viewed through the opacity. Such corneal opacities cause significant ↓ VA (worse than 6/18 vision) and, therefore, VA should be measured (➲ Colour plate 25e).

Box 12.6 WHO's 'SAFE' strategy for the global elimination of trachoma

S Surgery for entropion and trichiasis.
A for infectious trachoma.
F Facial cleanliness to reduce transmission.
E Environmental improvements, e.g. control of disease-spreading flies and access to clean water.

Xerophthalmia

Xerophthalmia is due to vitamin A deficiency, which may → corneal ulceration and blindness, especially with measles. A medical emergency, as severe vitamin A deficiency has a high mortality (➲ Vitamin A deficiency, p. 658). Patients with acute corneal lesions should be referred, whenever possible, to a hospital for treatment of their general condition, as well as their eye disease.

Ocular leprosy

Leprosy (➲ Leprosy, p. 439) can affect eyelids, cornea, or pupils by damaging nerves to eye or by causing iritis.

Eyelid

Nerve damage may occur during a type 1 reaction and cause an inability to close the eye (lagophthalmos), ↑ corneal exposure, ulceration, scarring, and blindness. In the acute stages, systemic treatment of leprosy reaction may restore nerve function.

Management

Protect cornea during sleep by applying ointment and strapping upper eyelid to cheek. If severe and permanent, or there is corneal ulceration, a tarsorrhaphy is required to protect cornea: sewing together lateral third of upper and lower eyelid margins.

Cornea

Ophthalmic nerve damage → corneal anaesthesia. Patient blinks less often and may be unaware of minor trauma to the cornea → ulceration, scarring, and blindness.

Management

Prevent by early recognition and educating patient to protect cornea during the day by blinking, and at night with ointment and strapping of eyelid to cheek. If these fail, then a lateral tarsorrhaphy is required.

Pupil

There may be acute anterior uveitis with a red painful eye, and small irregular pupil. This may accompany an erythema nodosum leprosum reaction. Leprosy also → chronic low-grade anterior uveitis in which the pupil is very small and irregular and will not dilate. Eye is usually white in chronic iritis.

Management

In acute anterior uveitis, pupil should be dilated immediately and patient kept on atropine and topical steroids. In chronic anterior uveitis, it is important to keep pupil dilated and maintain patient on mydriatic eye drops for life.

HIV infection and the eye

Ocular manifestations of HIV infection include:
- Herpes zoster ophthalmicus.
- Squamous cell carcinoma of the conjunctiva.
- CMV retinopathy.

Herpes zoster ophthalmicus

Presents initially with pain over one side of head and face → vesicular rash. Upper eyelids are always involved +/– keratitis and iritis, which can → ↑ IOP. Disease is often blinding in HIV+ve individuals with corneal involvement and severe intraocular inflammation. Treatment is with oral aciclovir 800mg 5×/d. Sometimes first sign of HIV infection, and all patients should receive counselling and HIV test.

Squamous cell carcinoma of the conjunctiva

A raised irregular white lesion, usually on temporal conjunctiva, that grows to invade fornices, lids, and cornea. Treat by wide surgical excision where possible. Adjuvant treatment with topical fluorouracil (5-FU) may reduce the risk of recurrence.

Cytomegalovirus

CMV retinitis is the commonest opportunistic infection of the eye and a major cause of blindness in advanced HIV (CD4 count <100). Where ART is available, CMV retinitis has become rare. The appearance is one of red haemorrhages and pale necrotic tissue ('cottage cheese and ketchup'). It is bilateral in 50%, slowly progressive, and can destroy whole retina. Treatment, if available, is with:
- Ganciclovir 5mg/kg IV every 12h for 2–3wks, then 5mg/kg/d *or*
- Foscarnet 60mg/kg IV tds for 2–3wks, then 90–120mg/kg/d.

However, both have severe side effects and are expensive. Alternatively, ganciclovir can be given by weekly intravitreal injection. This requires much lower doses, with little risk of systemic toxicity, but carries risk of introducing infection (endophthalmitis) and inconvenience of weekly intraocular injections.

Onchocerciasis and the eye

An infection of skin and eye due to filarial worm *Onchocerca volvulus* (➲ Onchocerciasis ('river blindness'), p. 578).

Inflammation can affect the:

- *Cornea*: → acute punctate keratitis, which may → sclerosing keratitis and corneal scars.
- *Iris*: → anterior uveitis and posterior synechiae.
- *Choroid and retina*: → chorioretinitis, night blindness, and chorioretinal atrophy (most marked temporal to the macula).
- *Optic nerve*: → optic neuritis and 2° optic atrophy.

No treatment can restore vision that has been lost due to onchocerciasis, but annual treatment with ivermectin prevents eye damage in endemic areas.

Malarial retinopathy

Malarial retinopathy is seen in severe malaria, occurring in >60% of patients with cerebral malaria, and carrying a worse prognosis (Colour Plates 35–38). It is common in children with cerebral malaria, so that if retinopathy is absent in a child thought to have cerebral malaria, bear in mind the possibility of other causes of coma, particularly if the coma is prolonged.

Erythrocytes infected by late-stage parasites of *Plasmodium falciparum* adhere to endothelium of brain and retina → microcirculatory arrest and vascular changes whose presence and severity predict the risk of death and length of coma. Malarial retinopathy resolves some time after the resolution of coma in cerebral malaria, leaving no persisting retinal abnormalities and no apparent effect on VA. Malarial retinopathy consists of one or more of:

- *Retinal whitening*: patchy opacification of the retina; can affect the macula (sparing the central fovea), or the peripheral retina.
- *Vessel changes*: discoloration of retinal vessels to orange or white, mainly in the peripheral fundus.
- *Retinal haemorrhages*: predominantly white-centred, intraretinal, blot haemorrhages similar to Roth spots. These can be extremely numerous and overlapping. Flame and large blot haemorrhages are also common.
- *Papilloedema*: reflects ↑ ICP, so is not specific to vertebral malaria. When papilloedema is present in isolation, consider other causes of coma.

Eye complications of Ebola virus disease (EVD)

EVD is described in more detail elsewhere (➲ Ebola and Marburg virus diseases, p. 746). Survivors of EVD may suffer late complications. Uveitis, of uncertain cause, occurs in up to 40% of survivors. It is possible that the virus persists in the eye → recurrent inflammation. Moreover, EVD disrupts the immune system, and this may → non-infectious uveitis. Anterior uveitis appears to be the commonest form, but posterior uveitis with associated retinal scarring has also been described (Colour Plate 38).

Following the EVD outbreak in W Africa, many survivors lost vision from uveitis, due to cataract, phthisis, and other complications. However, when the uveitis is treated promptly, with steroids and mydriatic drops, there is usually a full recovery of vision. EVD survivors should be warned of the risk of uveitis and to attend an eye clinic promptly if they develop a painful red eye.

Although Ebola virus has been recovered from the aqueous fluid of a patient with uveitis, other studies of EVD survivors have not demonstrated viral persistence in the eye. Cataract surgery in EVD survivors is safe and effective.

Other ophthalmic complications of EVD include optic neuropathy, and nystagmus. These are likely to be due to CNS involvement.

Dermatology

Robert Weiss

Introduction

The skin's main functions are:

- *Barrier against mechanical, thermal, and chemical injury, pathogens, and UV-damage*: extensive skin damage, e.g. burns or toxic epidermal necrolysis (TEN), may be fatal.
- *Sensation*: sense of touch, pain, itch, orientation, temperature, and pressure. ↓ protective sensation may → injury or pressure ulcers.
- *Thermoregulation*: control of cutaneous circulation and sweating prevents potentially fatal cooling and overheating.
- *Psychosocial*: healthy skin → 'look good, feel good' factor; skin disease may → depression, neglect, stigma, and ↓ personal and work prospects.

Common problems

Skin disease is among the top three reasons people seek healthcare, common problems being:

- Infections and infestations.
- Loss of skin: burns and ulcers.
- STIs affecting skin or mucosae.
- Dermatitis (eczema), psoriasis, and bullous disorders.

Management of skin disease with limited resources

Good skin care may be given using local resources at low cost.

- Take a full history incl. current medication, other medical conditions, and travel history; exposures to insects, plants, recent trauma, use of skin creams and similar (e.g. petroleum jelly), cleansing solutions, and environmental toxins.
- Carefully examine whole skin to enable pattern recognition. Daylight is best for skin examination. Feel skin for infiltration and temperature.
- Prevent further damage to diseased skin, e.g. from infection (keep wounds clean and ensure good hygiene) and from trauma. 'Off-loading' the skin is important in preventing pressure ulcers. Well-fitting shoes help prevent foot trauma. Hats provide protection from sun. A blanket may provide warmth, shade, and cover from flies; and injury from fire ↓ by education and safer cooking devices.
- Preserve and enhance barrier function with locally available moisturizers, such as emulsifying ointment, aqueous cream, and vegetable oils (apply to wet skin). White soft paraffin and mineral oils may cause irritation and 'trap' infectious agents but may be useful in dry skin conditions.

Psychosocial aspects of skin disease may significantly affect quality of life. Skin disfigurement, albinism, leprosy, smell of chronic ulcers, or cutaneous manifestations of AIDS may → stigma and depression. They also fuel a market in ineffective remedies; this and over-usage of cosmetics contribute to the cycle of poverty.

Infections of the skin

For soft tissue infections, see ➲ Chapter 14.

Folliculitis

Inflammation of the hair follicle, usually bacterial (*Staphylococcus aureus*), but fungi (*Malassezia* (formerly known as *Pityrosporum*)) may also be implicated, esp. in HIV/AIDS. Treat according with antibiotics or antifungals (imidazole cream bd or itraconazole or ketoconazole 200mg od for 1–3wks).

May be due to heat and friction where no infection is present.

Folliculitis keloidalis nuchae

A deep folliculitis of the posterior aspect of the scalp. It is common in African males. It is usually caused by staphylococci → to a chronic fibrosing folliculitis and peri-folliculitis. Keloidal scars are produced in the deeper cutaneous tissue. New papules and pustules occur at the rims of the keloid. The course is very chronic.

Treatment Doxycycline 100mg od oral for 2wks to several months. Combine with potent topical steroid, e.g. betamethasone cream bd on lesions or intralesional steroids. Full-thickness excision of scars left to heal by 2° intention leaves an atrophic scar with no recurrence.

Acne

Blocked sebaceous gland ducts (forming comedones = blackheads and whiteheads), which may → inflammatory papules, pustules, nodules, and scarring. It commonly occurs on the face and the upper trunk. It may be very mild to very severe. In severe acne, cysts and scar formation result. It is very common in puberty, usually ↓ in early adulthood. Adult acne is commoner in females. In dark skin, post-inflammatory hyperpigmentation may cause distress. To prevent this, inflammatory acne should be treated at an early stage.

Management

Stop the use of white soft paraffin, oil, or ointments and greasy cosmetics, which further block sebaceous ducts.

'Peeling' of comedones with benzoyl peroxide gel, benzoyl peroxide + adapalene gel, or tretinoin 0.01–0.1%; apply at night since both are photosensitizers. Beware of irritating the skin as this may result in post-inflammatory pigmentation. An alternative is salicylic acid 1–10% +/−sulphur praecipitatum in a cream, gel, or alcoholic solution. Alcoholic solutions remove excess sebum, e.g. dilute methylated spirits with an equal amount of water to give a 35% solution.

For pustular/inflammatory lesions: add topical clindamycin 1% lotion, erythromycin 2% lotion, or use doxycycline 100mg bd until substantial improvement (may be 2–3mths or more) followed by 100mg od until acceptable or cleared, which may take many months. Avoid doxycycline in children <12yrs or pregnant females.

Other antibiotics are sometimes used such as dapsone or co-trimoxazole. Hormonal approaches using antiandrogenic contraceptive pills are useful in selected females. For very severe cases, use of isotretinoin may be indicated—refer to a specialist.

Skin infestations

Arthropod bites are a common cause of itch. Papular urticaria, excoriated areas, and even blisters may result in sensitive individuals.

Heavy mite or louse infestations may occur in the immunocompromised and the deprived. An itch–scratch cycle → 2° pyoderma. Treat household contacts. Bites from gnats, blackfly, and midges are best prevented by thick clothing.

Lice

There are three species of medical importance; the first two look identical:

- Head louse (*Pediculus humanus capitis*).
- Body louse (*P. h. corporis*)—the vector of epidemic typhus (*Rickettsia prowazekii*), relapsing fever (*Borrelia recurrentis*), and trench fever (*Bartonella quintana*).
- Pubic or crab louse (*Pthirus pubis*).

Transmission is by close personal contact. Lice pierce the skin to take a blood meal, injecting saliva and defecating at the same time. Hypersensitivity reaction to the saliva → rash. Body lice live in the host's clothes, passing onto the skin only to take a blood meal; head and pubic lice infest hair-bearing skin. Eggs ('nits') are laid and firmly glued to hairs. Enlargement of the occipital lymph glands are often present in children.

Management

Body lice are easily dislodged from clothes, but leave eggs in bedding, towels, and clothing. Launder clothes in a very hot wash, then iron the seams; or dust clothes with 1% malathion powder.

For head and pubic lice, apply 0.5% malathion liquid on the affected parts, allow to dry naturally, and remove by washing after 12h. (Alternatives to malathion: carbaryl 0.5–1%; permethrin 5%; phenothrin 0.2–0.5%; ivermectin 0.5% lotion.)

Scabies

Sarcoptes scabiei (➲ Colour plate 19a–c) is transmitted by close personal contact. The female burrows into the epidermis to lay eggs; burrows are seen as 0.5–1.5cm long irregular tracks often on the web spaces of the fingers Sensitization to mite faeces and saliva occurs within a few weeks of 1° infestation. Reinfestation results in almost immediate irritation and sometimes a generalized urticaria.

Itchy papules and linear burrows occur in a symmetrical distribution, esp. in the finger webs and on the flexor surface of the wrists (frequent hand washers have fewer lesions on the hands). Other common sites: elbows, axillae, genitalia (particularly scrotum), peri-umbilicus, and breasts. Head and plantar involvement is common in infants, but unusual in older age groups. Macules and pustules occur. Scratching → 2° bacterial infection. Severe, hyperkeratotic ('Norwegian') scabies occurs in immunocompromised (e.g. HIV+ve) individuals. Hundreds of mites are present in these cases and spread is common.

Management

Apply permethrin 5% cream, malathion 0.5%, or benzyl benzoate 25% to the body and leave on for 24h before washing off; repeat after 1wk.

Benzyl benzoate is applied on 3 consecutive days and may require repeated applications to penetrate crusts. Sulphur 2–10% creams may be used overnight to soften the crusts (also safe in babies).

Ivermectin 200 micrograms/kg oral stat is an alternative, esp. for Norwegian scabies, or communities (e.g. prisons). All clothing worn the previous day, the day of the treatment, and all bedding, must be washed. Iron the laundry or dry for an hour in a hot dryer. Place any un-washable items into a closed plastic bag for 2wks. The eggs will hatch in ~10d, but mites will die if away from human skin for > 24h. Asymptomatic infection is common, so treat the whole household. *Note*: itching may persist for days, but does not usually indicate treatment failure.

Trombiculid mites (chiggers)

Chiggers are the larvae of trombiculid mites, several species of which may → itchy dermatitis. Tiny larvae assemble at the tips of foliage and attach to passing mammals, birds, and humans, feeding on the host tissues. Typically, an itchy dermatitis occurs within a few hours of walking through long grass or other vegetation. Application of repellents, e.g. diethyltoluamide (DEET), to skin and clothing will help prevent chigger attack.

Ulcers

Ulcers = absence of surface layers of skin. They are prone to infection and require a greatly ↑ blood supply for repair. Healing may be ↓ by: local factors in and around the wound; general ill health; and/or lack of access to care. 2° infection by *Streptococcus pyogenes* or *Staphylococcus aureus* is common. Fig. 13.1 illustrates the causes of ulcers.

Neuropathic (pressure) ulcers

These are due to a prolonged compression of the blood supply. They occur in the sick and elderly or neurological deficits, e.g. paraplegia, diabetic neuropathy (➲ Peripheral neuropathy, p. 438), or leprosy. The latter two may → the 'neuropathic foot'. Pressure ulcers are preventable with frequent off-loading, and by encouraging movement. Skin care with washing and emollients and gentle movement is beneficial since it ↑ barrier function and ↓ entry points for bacteria and irritants. Supply pressure-relieving footwear. Leprosy may → neuropathic ulcers and leprosy reactions may rarely ulcerate—see ➲ Leprosy, p. 439. Consider leprosy when 'spontaneous' ulceration appears on hands or feet.

Venous ulcers

Damage to venous valves by stasis, trauma, or thrombosis → venous (+/− lymph) stasis → oedema, compromising the skin by ↓ O_2 and nutrients. Risk factors: obesity, advanced age, and immobility. Less common in those who frequently sit cross-legged on the ground or actively use their legs. Arterial ulcers occur due to peripheral vascular disease. Risk factors: smoking, diabetes, and advanced age.

Sickle cell disease

Contributes to ulceration of the lower leg, esp. the ankle, often beginning in early adolescence. The cause is often mild trauma, complicated by obstruction of small blood vessels by the sickling cells.

Tropical ('phagedenic') ulcer

This is a necrotic lesion caused by the synergistic action of anaerobes (*Fusobacteria ulcerans*) and *Treponema vincentii*. It occurs where legs are repeatedly damaged by vegetation, e.g. acacia thorns. A painful necrotic ulcer develops from a small papule; it mainly affects children and young men, e.g. farmers. After a few weeks, the ulcer stops spreading as inflammation and pain ↓. Some ulcers heal spontaneously leaving a scar; others become chronic and may persist for years. Noma (cancrum oris) is a phagedenic ulcer of mouth.

Anthrax

Contact with an infected animal or infected hides etc. → inoculation with *Bacillus anthracis*. Itching → papule with a dark central vesicle after hours to days → enlarges to form characteristic necrotic eschar surrounded by a rim of vesicles. Not painful; typically surrounded by extensive non-pitting oedema.

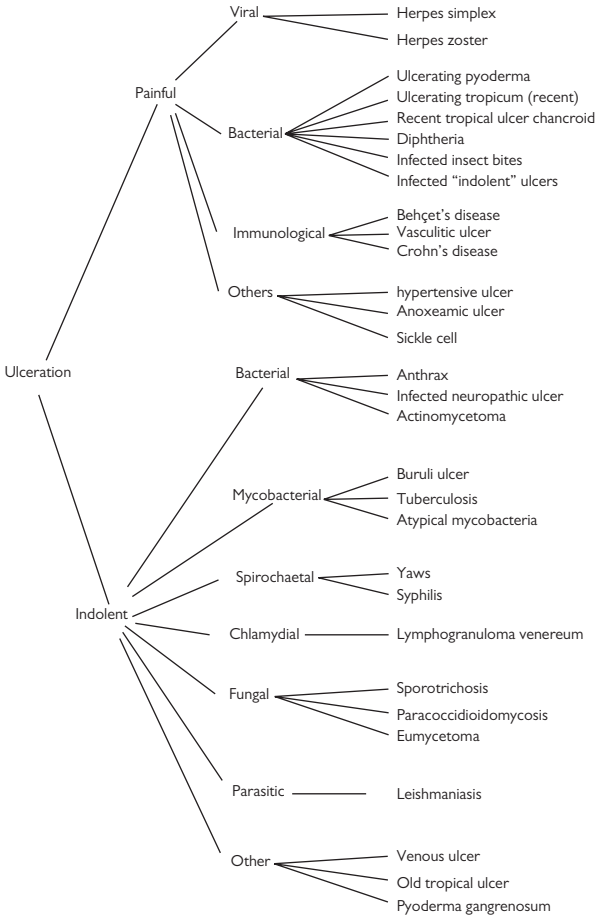

Fig. 13.1 Classification of skin ulcers.

Mycobacterial ulcerating diseases

Buruli ulcer (BU)

Caused by *Mycobacterium ulcerans*, is the third commonest mycobacterial disease (after TB and leprosy) in HIV–ve individuals (➲ Colour plate 12). It is common in children. BU was first described in Uganda and is endemic in swampy areas in W Africa. BU may be seen elsewhere in the tropics. *M. ulcerans* probably resides in muddy water, and is inoculated into skin

by minor injuries → a painless papule, plaque, or nodule → fluctuates after 1–2wks → slowly ulcerates forming a chronic painless ulcer with extensive undermined edges. The patient is not systemically unwell and there is no oedema. Mycolactone, a bacterial exotoxin → necrosis; ulcers may spread rapidly → very large and disfiguring and 2° infection may occur → sepsis, tetanus, and death. Deeper structures may be involved, e.g. osteomyelitis.

Management

- Prevent 2° infection.
- Treat with: 8wks rifampicin + 4wks streptomycin + 4wks clarithromycin; or 8wks rifampicin + 8wks clarithromycin.
- BU may heal spontaneously → severe scarring and contractures; skin grafting may be needed.

Tuberculosis

Cutaneous TB (lupus vulgaris) may → papules, plaques, warty lesions, cold abscesses, and chronic ulceration. Erythema nodosum and Bazin's disease, both forms of panniculitis (sometimes ulcerating) occur on lower legs.

Treatment Standard TB treatment, see ➲ Tuberculosis treatment, p. 156.

Other causes of ulcers

These include cutaneous diphtheria, cutaneous leishmaniasis (➲ Cutaneous leishmaniasis, p. 568, see Colour Plate 13), sexually transmitted infections (➲ Sexually transmitted infections, p. 603), non-venereal treponematoses, actinomycosis, deep mycoses, chronic osteomyelitis, dracunculiasis, trypanosomal chancre, the eschars of rickettsiae, and Behçet's disease.

When an ulcer does not heal, consider *pyoderma gangrenosum*, which may or may not be associated with IBD, RA, and myeloproliferative diseases. Small nodular pustules → large ulcers at various sites, not healing with antibiotics and worsened by trauma.

Management of ulcers

- Identify the cause.
- Clean the wound carefully of pus and slough. Cover the ulcer and cover with moist (not wet) dressings with saline. As water evaporates, saline concentration in dressing ↑ → wound secretions and debris to be extracted. Change dressings every 6h wound until clean. Alternatively, clean with 1–6% hydrogen peroxide or dilute sodium hypochlorite solution (0.5% available chlorine) at each dressing change.
- Apply clean dressings using short pieces of bandage or well-washed linen. Use dressings with saline or impregnated with honey, coconut oil, or white soft paraffin, and cover to prevent evaporation; this will soften crusts and encourage healing. Hydrocolloid dressings may not be suitable in humid climates.
- Avoid adherent dressings. When removed, these → pain and bleeding, and tear off new healing epidermis. Wash and apply emollient on surrounding skin, avoiding maceration of healthy ulcer border with zinc oxide cream, ointment or paste.
- Blood supply to the ulcer should be optimized by ↓ pressure and ↑ exercise. Treat 1° or 2° bacterial infection. Address conditions → poor healing, e.g. malnutrition.

- Delayed healing often results from FBs, pus, necrotic tissue, and sequestra, which must be removed. Dead tissue can be excised without pain. Local application of honey or aloe vera ↑ wound healing, but in general, herbal remedies should be avoided.
- Large/chronic ulcers may require excision and/or grafting.

Tropical ulcer: in addition to above-listed measures, give procaine benzylpenicillin 0.6–1.2g IM daily for 3–7d.

Anthrax: treat with penicillin, ciprofloxacin, or doxycycline (➲ p. 718).

Rashes

Rashes may be itchy or non-itchy, monomorphic or polymorphic, acute or chronic, symmetrical or asymmetrical, and localized, regional, or generalized. They may be comprised of macules, papules, plaques, vesicles, pustules, wheals, scales, erosions, or petechiae. See Box 13.1.

Basis of rashes and topical treatment

- In dark skin erythema is not visible, but looks hyperpigmented: palpate to feel inflammation.
- Lesions differ according to depth of inflammation. Near surface → vesiculation and scaling, while deep dermal or subcutaneous inflammation → nodules and plaques.
- Rate of development is determined by type of inflammatory response. Erythema, wheals, and blisters are more acute; white cell infiltration, purpura, and pustules take longer; while ischaemic necrosis and exfoliation are more chronic.

The distribution of the lesion may be typical—see Figs. 13.2 and 13.3.

Endogenous rashes (e.g. psoriasis) tend to be symmetrical; in contrast, exogenous causes (e.g. a biting insect or fungal infections) → asymmetric lesions.

Topical treatments

- Use creams for wet and acutely inflamed lesions.
- Use ointments (oily) for chronic, dry, or lichenified lesions.
- Use topical steroids only for short periods; or intermittently, e.g. 4d per wk during longer periods. May be diluted with white soft paraffin or vegetable oil.

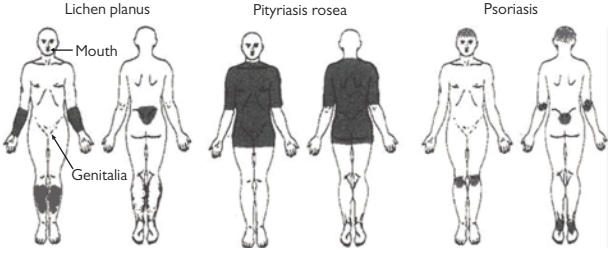

Fig. 13.2 Characteristic distributions of lichen planus, pityriasis rosea, and psoriasis.

Box 13.1 Common rashes (* = itchy)

Maculopapular

Extensive	Sparse
• Dermatitis*/eczema.*	• Typhoid rose spots.
• Body lice.*	• Gonococcal.

- 2° syphilis.
- Flea bites.*
- Scabies.*
- Lichen planus.
- Rubella.*
- Pityriasisrosea.+/−*
- Measles.+/−*
- Drug eruption.*

Hypopigmentation

- Post-inflammatory.
- Pityriasis alba.
- Leprosy.
- Tinea versicolor.
- Pinta.
- Yaws.
- Vitiligo.
- Post-kala azar dermal leishmaniasis.

Nodules

- Onchocerciasis.
- Leprosy.
- Gouty tophi.
- Fungal infections.
- KS.
- Erythema nodosum.
- Cutaneous leishmaniasis.

Plaques/crusts

- Fungal infections.
- Psoriasis.
- Impetigo.
- KS.
- Trypanosomal chancre.
- Pinta.
- Cutaneous leishmaniasis.
- Crusted scabies.
- Eschar (*Rickettsia*).

Urticaria*

- Drugs.
- Strongyloidiasis.
- Loiasis.
- Gnathostomiasis.
- Schistosomiasis (Katayama fever).

Vesicles

- Chickenpox.
- Monkey pox.
- Orf.
- Herpes zoster.
- Papular urticaria.
- Vasculitis.
- Herpes simplex.

Pustules

- Bacterial infection.
- Psoriasis.
- Gonococcaemia.
- Irritant folliculitis.

Petechiae

- Meningococcaemia.
- Vir al haemorrhagic fevers.
- Typhus.
- Causes of DIC.

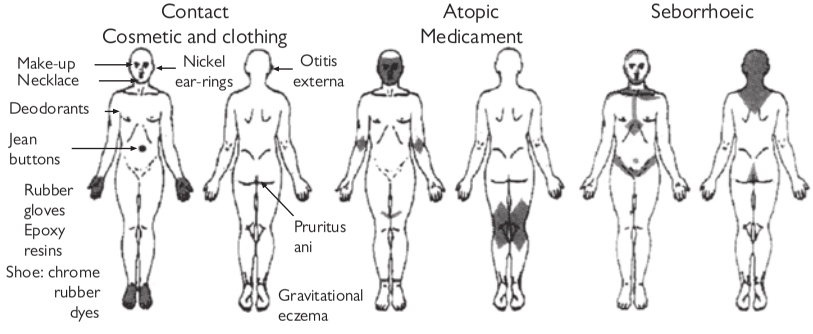

Fig. 13.3 Common patterns of dermatitis/eczema.

Dermatitis (eczema)

Inflammatory reaction of the skin that may occur as a (usually asymmetrical) response to an external irritant; or as a symmetrical rash to an endogenous stimulus. For management, see Box 13.2.

Atopic eczema

Atopy is a genetic predisposition to (IgE-mediated) hypersensitivity reactions: asthma, hayfever, and atopic eczema. Atopy affects 10–20% of children, esp. in urban settings. Whole skin is dry and itchy, lesions are itchy, red, with fine scaling, excoriated and lichenified from scratching and easily superinfected. Deteriorates with dryness, superinfection, heat, sweating, contact with allergens or irritants, and emotional stress. Common on face, flexures, hands, and feet. Differentiate from scabies.

Seborrhoeic eczema

Greasy yellowish scaling and erythema in seborrhoeic areas of skin: scalp, eyebrows, nasolabial folds, presternal, axillae, and groins. Severe, often superinfected seborrheic eczema is characteristic of HIV infection. May be in folds around neck and scalp involvement in infants <4mths.

Irritant contact dermatitis

Commonly affecting hands in contact with irritants at work; also affects feet of barefoot agricultural workers. Skin is dry and breaks easily. Previously damaged skin or atopic skin ↑ susceptibility to irritants.

Allergic contact dermatitis

Sensitization to an allergen, normally over months or years, → onset of dermatitis within hours of subsequent exposure to the allergen (e.g. cosmetics, nickel in zips, belt buckles, buttons, stainless steel watches, or jewellery, food, plants, medicines, metals). Irritant dermatitis is a risk factor for allergic contact dermatitis. Patch testing identifies allergen: suspected allergens are applied to normal skin, usually on back, and examined at 48h (24h in hot and humid conditions) and 72h for redness, swelling, or vesiculation.

Lichen simplex

Usually a single lichenified (thickened) eczematous patch, which is perpetuated by habitual scratching or rubbing. Common in the neck, groins, shins, lower arms, and around the ankles.

Box 13.2 Management of dermatitis (eczema)

- Explain chronic, recurrent nature of the condition.
- Eliminate or avoid known irritants/allergens. White soft paraffin may act as an irritant.
- Avoid soaps (these dry the skin); wash instead with emollients, (e.g. aqueous cream) to keep the skin hydrated.
- Moisturize skin daily with emulsifying ointment or cetomacrogol cream, or vegetable oil (e.g. coconut oil).
- Treat acute weeping eczema with creams, and chronic lichenified eczema with ointments.
- Apply topical steroids to affected areas 1–2× daily. Use the weakest effective steroid, for short periods of time or intermittently (4d per week). A weak steroid (e.g. hydrocortisone 0.5–1%) can be used on face or in flexures. Avoid strong steroids in children. Strong steroids can be diluted with white soft paraffin or vegetable oil.
- *Seborrhoeic eczema*: add imidazoles and/or sulphur 5–10% and/or salicylic acid 2–5% to a base cream or steroid cream.
- Severe chronic eczema: apply coal tar ointment (2–10%) or paste or strong topical steroids to relieve itch. Covering (e.g. with zinc oxide adhesive plaster) may be necessary.
- Stop scratching! Give topical treatment and sedating antihistamines at night (not age <2yrs).
- Refractive cases can be helped by prednisolone and other steroid-sparing immunosuppressive drugs (e.g. azathioprine).
- Treat 2° bacterial infection: topical povidone-iodine or gentian violet, weak potassium permanganate solution, or antibiotics (e.g. cloxacillin or erythromycin).
- Breastfeeding may ↓ risk of atopic eczema. Emphasize if a family history of eczema.

Psoriasis

Psoriasis is a disease of skin, nails, and joints (Box 13.3) which affects ~1–2% of western populations, less common in tropics. It is aggravated in HIV/AIDS.

- *Classic plaque psoriasis*: sharply demarcated silvery plaques with large scale and +ve candlewax/silvery scale phenomenon (scratch → whiteness). Plaques are common on knees, elbows, lower back and scalp/hairline.
- *Inverse psoriasis*: red, shiny lesions with little scale, often with fissures and maceration in navel, natal cleft, armpits, groins.
- *Guttate psoriasis*: small, poorly defined lesions (often red with little silvery scale) that occur across the whole body; often in adolescents after streptococcal sore throat or vaccination.
- *Palmar/plantar psoriasis*: lesions develop deep cracks and sterile pustules; nails often involved. Differentiate from fungal infection.
- *Generalized pustular psoriasis*: fever, arthropathy, bright red erythema → development of multiple pustules. Can occur after stopping steroids. Resolves spontaneously.

Psoriatic arthritis occurs in ~10% of patients. Five patterns are recognized: a small joint arthritis of hands and feet with distal interphalangeal joint involvement (most common); seronegative rheumatoid-like arthritis; large joint mono- or oligoarthritis; spondylitis; and arthritis mutilans.

Box 13.3 Management of psoriasis

Chronic condition, partly responsive to agents that ↓ cell turnover and partly responsive to immunosuppressive therapy. Treatment options are:

- *Emollients*: e.g. urea 10% ointment or white soft paraffin restore barrier function and ↓ dryness. Keratolytics, e.g. salicylic acid 5–10% ointment.
- *Strong topical steroids*: e.g. betamethasone dipropionate 0.05% or clobetasol propionate 0.5% od for thick lesions (use with care as may cause rebound), mild steroids, e.g. hydrocortisone 1% or triamcinolone 0.1% in flexures.
- *Coal tar derivatives* (5–10%) and dithranol (0.1–3%): start at a low concentration and gradually ↑; may be combined with UV exposure.
- *Severe and/or widespread psoriasis, psoriasis with arthritis*: methotrexate 5–20mg once weekly + folic acid 5mg daily on other days. May be used in HIV+ve individuals. Monitor liver function, avoid pregnancy.
- *Biologics*: expensive.
- In general, systemic corticosteroids should be avoided (rebound).

Pityriasis rosea

Pityriasis rosea is a viral infection of young adults. A flu-like prodromal episode → a single annular erythematous and scaling 'herald patch' appears on trunk or arms (may be confused with ringworm) → within a week by an erythematous and variably pruritic rash of the trunk which typically follows skin lines (Christmas tree pattern). Rash resolves spontaneously in weeks to months. Exclude syphilis.

Lichen planus

Itchy, flat-topped, shiny, purplish papules; may have fine white 'Wickham's striae' on the surface; appear on wrists, lower legs, and lower back; lacy white lesions +/– erosions may also occur on the buccal +/– genital mucosa. May resolve spontaneously over months, but mucosal and pretibial hypertrophic lesions last for years. May respond to strong topical steroids or be very refractive to treatment.

Drug eruptions

Drug eruptions may follow many conventional drugs or alternative remedies, usually >5–10d (up to 3wks) after first exposure. May occur within days after taking a drug in case of previous exposure. Usually symmetrical; exfoliation or vesiculation are rare; commoner in HIV+ve individuals.

Exanthems

Are most common, may be maculopapular, urticarial, purpuric (also see ➲ Vasculitis, p. 554). Incidence >1% in penicillins, sulfonamides, NSAIDs, isoniazid, erythromycin, hydantoin derivatives, carbamazepine.

Fixed drug eruption

Occurs at same (fixed) site following a particular drug (e.g. sulfonamides, tetracyclines, muscle relaxants). May blister within a few hours of intake and it leaves a round pigmented mark.

Management

- Ask about previous reactions to drugs.
- Stop all implicated drugs.
- Give prednisolone 30–60mg tapering down quickly, if reaction is acute/severe.
- Stevens–Johnson syndrome (SJS) and TEN: stop all potential drug triggers. Nurse as for extensive burns, attending to fluids, nutrition, and prevention of 2° bacterial infection to prevent high mortality from fluid loss. Steroids may ↓ progression, but later significantly ↑ risk of infection/sepsis through missing skin. High-dose, short-course steroids are sometimes given in first days of the disease. IVIg may be of benefit. TEN is associated with a high mortality (Box 13.4).
- Never reintroduce drugs that have caused anaphylaxis, TEN, or severe exfoliative dermatitis. In mild cases, restart only essential drugs one by one to identify causative drug.

Box 13.4 Stevens–Johnson syndrome

SJS is a severe form of erythema multiforme (➲ Erythema multiforme, p. 557) complicated by severe blistering of skin and mucosae including the mouth, eyes, and genitalia, and accompanied systemic features such as fever. Target lesions of erythema multiforme may be evident, but in its most severe form TEN → widespread blistering and loss of the skin. This is associated with a +ve Nikolsky sign, where the top skin layer is rubbed off with light pressure; see ➲ Fig. 13.5, p. 559. Complications include diarrhoea, adhesion of eyelids to conjunctivae, anterior uveitis, pneumonia, renal failure, and polyarthritis. Triggers include drugs, e.g. sulfonamides, thioacetazone, nevirapine in HIV+ve individuals, allopurinol, streptococcal infections, viral infections (e.g. HSV, Orf), malignancy, and some systemic diseases (e.g. SLE).

Vasculitis

Cutaneous vasculitis may occur in isolation or as part of systemic vasculitis. Vessel wall damage may → urticaria, palpable purpura, ulcers, necrosis, livedo reticularis. Superficial lesions may be vesicular/blistering; deep lesions nodular (e.g. erythema nodosum) and occasionally suppurating. Urticaria occurs more commonly in infants, necrosis more commonly in adults. (*Note*: bruising and non-palpable purpura suggest platelet deficiency.)

Prognosis of vasculitis depends on vital organ involvement. Monitor for haematuria as a sign of renal involvement (Box 13.5). Most patients need to be referred for specialist evaluation and treatment. Look for and treat any identifiable cause (e.g. infection). NSAIDs may help (caution in renal impairment). Consider corticosteroids if multiorgan involvement and fever (caution in severe infections). Azathioprine or cyclophosphamide may be used in severe disease, and dapsone in leukocytoclastic vasculitis.

Box 13.5 Henoch–Schönlein purpura

Henoch–Schönlein purpura is a syndrome of vasculitis (usually manifest as palpable purpura affecting the legs and buttocks), arthralgia, periarticular oedema, abdominal pain, +/− IgA glomerulonephritis, common in children. IgA immune complexes are thought to be produced by a common infection (e.g. viral pharyngitis) in genetically susceptible individuals. Complications include GI bleeding, intussusception, nephritic and/or nephrotic syndrome; rarely protein-losing enteropathy, orchitis, or CNS involvement. Henoch–Schönlein purpura is usually self-limiting. Haematuria, indicating renal involvement, must be monitored during 12mths after Henoch–Schönlein purpura.

Erythema nodosum

A form of panniculitis presenting as symmetrical, tender, erythematous nodules on shins or forearms (for causes, see Table 13.1). Exclude TB (incl. latent TB), sarcoid, streptococcal sore throat, leprosy reactions, and inflammatory bowel disease. Treatment is symptomatic (analgesia). Most lesions resolve spontaneously over several days.

Table 13.1 Causes of erythema nodosum

Infections	• Streptococci • Tuberculosis • *Chlamydia* • *Yersinia* • Histoplasmosis • Leprosy*
Drugs	• Sulfonamides • Sulfonylureas • Oral contraceptive • Aspirin • Phenytoin • Dapsone
Sarcoidosis	
Inflammatory bowel disease	
Rarer causes include Behçet's disease, rheumatic fever, pregnancy	

* See ➲ Box 9.24, p. 443 for ENL.

Urticaria

Itchy, transient wheals (swelling and flushing of the skin), lasting 30min–24h, although new lesions may continue to develop. May be accompanied by joint pains, stomach aches, and fever. Eosinophilia rare unless worm infections present.

Causes

Allergens (e.g. food, drugs, helminths) bind IgE → release of histamine → dermal oedema.

- Immune complex disease and complement activation (e.g. antivenom, penicillins, infections).
- Direct effect of histamine releasers in the skin (e.g. morphine, shellfish).
- *Urticarial vasculitis*: lesions may be delayed in onset, last hours to days, and become purpuric.
- *Angio-oedema*: oedema extends into the subcutaneous tissues. Larger, more solitary lesions lasting 4–48h may occur, and → dramatic swelling of the eyes, lips, and oropharynx.
- *Chronic idiopathic urticaria*: recurrent urticaria over >3mths. In most cases no cause is found.
- *Papular urticaria*: itchy and persistent papules following damage to epidermis, often by insect bite. Lesions intensely pruritic; may blister.
- *Dermographism*: immediate wheal and flare response to pressure or scratch.

Urticaria may be life-threatening when:

- It is part of an anaphylactic reaction.
- Angio-oedema compromises the airway.
- It is part of a severe systemic disease (e.g. septicaemia, SLE).

Management

Identify and remove/treat cause. Worm infections (e.g. strongyloidiasis) are rarely the cause, but if present will generally also produce eosinophilia.

Give antihistamine (e.g. chlorphenamine 4mg oral 4hrly; desloratadine up to 4× normal dose). Steroids may ↓ airway inflammation in angio-oedema. Treat anaphylaxis as described on ➲ Shock, p. 322. Chronic urticaria may require H_2 antagonists (cimetidine, ranitidine) or even prednisolone, ciclosporin, or dapsone.

Erythema multiforme

Lesions of erythema multiforme vary, but include characteristic 'target lesions'—round, erythematous areas with pale or dusky, and sometimes vesicular centre. Rash is symmetrical and typically involves extensor surfaces and the palms and soles. It is usually self-limiting. For causes, see Table 13.2.

Table 13.2 Causes of erythema multiforme

Infections	• Herpes simplex • *Mycoplasma* • Orf • Mumps • Streptococci • Viral hepatitis
Drugs	• Sulfonamides • Sulfonylureas • Tetracyclines • Thiazides • Aspirin • Phenytoin • Carbamazepine • Alopurinol
Connective tissue diseases: e.g. SLE	
Malignancy	
Radiotherapy	

Blistering disorders

Blistering diseases are common. Clinical signs depend on cause and level of split in the skin (Fig. 13.4). Causes incl. burns, acute dermatitis from irritants/allergens, infections (e.g. impetigo, fungal infections of the foot), drugs (SJS/TEN; ➲ Box 13.4, p. 553), autoimmune diseases (pemphigus, pemphigoid, dermatitis herpetiformis), and genetic disorders (e.g. epidermolysis bullosa, porphyria). Autoimmune blistering disorders may be triggered by underlying malignancies or infection or drugs.

Pemphigus vulgaris

Causes fragile, intraepidermal blisters in adults. They commonly first appear in the oral and/or genital region before spreading all over the body. The blisters are flaccid (may be more tense in African patients) and enlarge when pressed. The roof can easily be rubbed off (Nikolsky sign, Fig. 13.5).

Treatment High-dose steroids (prednisolone 60–100mg daily), gradually ↓ as blistering resolves (5mg every 10th day). If new blisters appear ↑ dosage again. Mortality is 20–100%, even when treated.

Pemphigus foliaceus (PF)

Relatively common in rural areas in adults. Very superficial blisters, just beneath the stratum corneum, break easily and → well-demarcated scaly, crusted lesions, +/– pustules. (Differential diagnosis: impetigo.) Erosions can be painful and extensive, PF may become erythrodermic. Fogo selvagem ('wild fire') is an endemic variety of PF in Brazil thought to be caused by sensitivity to saliva of a *Simulium* blackfly. Other endemic variants may have similar aetiologies.

Treatment Potent topical steroids or oral dapsone may suffice although often systemic immunosuppressant therapy (prednisolone, methotrexate) is required.

(Bullous) pemphigoid

Subepidermal blisters, tense and frequently partially blood-filled, appear on clinically involved itchy erythematous skin and on normal skin. Antibodies are found along the basal membrane, Nikolsky sign is –ve. Pemphigoid is a disease of the elderly.

Treatment Potent topical steroid cream, e.g. clobetasol propionate 0.5% od to bd. More extensive cases respond well to systemic steroids (40–60mg prednisolone); titrate dose according to the blistering activity. Erythromycin or doxycycline 100mg bd plus nicotinamide 500mg tid may be effective as a steroid-sparing option.

Chronic benign bullous disease of childhood (juvenile dermatitis herpetiformis)

Chronic (linear IgA) blistering disease with acute onset in children. Small and large blisters appear predominantly on the lower trunk, genital area and thighs, on the scalp, and around the mouth. New blisters form around the old healing blisters forming a 'string of pearls'. (Differential diagnosis: consider impetigo.) Treat with dapsone.

Dermatitis herpetiformis

Characterized by intensely itchy rash with papules and vesicles over extensor surfaces. Typical lesions are herpetiform (grouped) arranged vesicles. Coeliac disease often associated. Treat with gluten-free diet and dapsone.

Epidermolysis bullosa

An inherited or acquired adhesion weakness at the dermal–epidermal junction causing subepidermal blisters, ranging from mild to severely mutilating or lethal forms. Inherited forms start early in life. All forms → blisters after minimal trauma; 2° infection is common and malignancies may occur in chronically scarred areas.

Porphyria cutanea tarda

Disturbance of porphyrin metabolism in patients with liver disease (e.g. chronic hepatitis C infection, alcohol abuse) → skin lesions. Exposure to sun or trauma → blistering, erosions, crusts, small depressed scars, and pigmentation changes. Alcohol or iron intake are triggers. Sometimes when urine is exposed to light it turns red.

Treatment Sun protection, abstain from alcohol, phlebotomy. Low-dose chloroquine (e.g. 150mg weekly) may be tried; in higher dose it may exacerbate the disease.

Fig. 13.4 Diagrammatic cross-sections of skin blisters. Left: pemphigoid, in which blister is thick-roofed. Right: pemphigus, in which the blister is thin-roofed and fragile.

Fig. 13.5 Nikolsky sign—blister roof rubbed off with light pressure.

Connective tissue diseases

Lupus erythematosus

An autoimmune disease in which autoantibodies are directed against DNA and complement is activated → damage to blood vessels, dermal–epidermal junction, and epidermis. Sun may initiate and ↑ disease in genetically predisposed individuals.

Chronic discoid lupus erythematosus (CDLE)

Lesions occur in sun-exposed areas, e.g. forehead, nose, and cheeks ('butterfly' pattern rash), chest and back, and extensor surfaces of the arms. Scaly with follicular plugging and atrophy with hyperpigmentation and depigmentation. In lighter skins, erythema can be seen. Lesions heal with scarring, and alopecia may follow scalp lesions. CDLE may → SLE in 2–20% (➲ Systemic lupus erythematosus, p. 689).

Management Sun protection essential. Strong topical steroids and hydroxychloroquine are standard treatment. Methotrexate and methylprednisolone pulse therapy are alternatives.

Subacute cutaneous lupus erythematosus (SCLE)

Polycyclic erythematous lesions with central depigmentation are seen in the sun-exposed areas. Patients are very sensitive to UV exposure, hence commoner in tropics. Generalized symptoms may be present, most notably tiredness. Very few develop SLE. Lesions heal without scarring.

Treatment Methylprednisolone pulse therapy; thalidomide; chloroquine or methotrexate.

Scleroderma

Sclerosis of the skin is a manifestation of mixed connective tissue disease (MCTD). In rural clinics, diagnosis is clinical.

Morphea

Circumscribed scleroderma. Dermis is markedly thickened. There may be a single or multiple plaques on the trunk, which progress over 3–5yrs and then stabilize.

Treatment Potent topical steroids or vitamin D derivatives (e.g. calcipotriol ointment) may be helpful.

Systemic scleroderma

Characterized by atrophy and sclerosus of the skin. Cutaneous vasculitis may → ulceration and necrosis of digits → claw-like hands. Facial movements (e.g. mouth opening) ↓ until the face becomes expressionless. Untreated, the condition progresses slowly.

Treatment Systemic steroids, methotrexate, cyclophosphamide, chloroquine.

Mixed connective tissue disease

Overlap occurs among RA, Sjögren's syndrome, SLE, scleroderma, and polymyositis. Diagnosis is made by clinical features and when possible by specific antibodies tests are useful, although none are 100% specific. Patients are typically female and may show features of SLE, systemic sclerosis, dermatomyositis, and polymyositis. Some arthritis or arthralgia is usually present. Fingers may be typically sausage-shaped due to swelling of the joints. Muscle weakness and pain are common. Raynaud's phenomenon may occur despite a warm climate.

Disorders of pigmentation

Skin pigmentation is mainly due to endogenous pigments: melanin, haemosiderin and bilirubin. Some common causes of hyper- and hypopigmentation are given in Boxes 13.6 and 13.7.

Hypopigmentation

Melanin is produced by melanocytes and transferred to keratinocytes. Loss of keratinocytes (exfoliation) → hypopigmentation, so skin is often paler following inflammation. When due to mildly dry skin, chapping, or eczema, it is termed *pityriasis alba*. Typically occurs on face and limbs in darker skinned children.

Treatment Reassure parents that it will clear in time. Apply emollients. Use sunscreens.

Pityriasis versicolor

Also called *tinea versicolor*, is due to *Malassezia ovalis* (also known as *Pityrosporum ovale*) and other yeasts, which → sharply defined confluent slightly scaly patches of hypopigmentation/brownish/reddish pigmentation, esp. of upper trunk. Common in humid climates, immunodeficiency.

Treatment Appy selenium sulfide shampoo daily for 1wk: apply lather, and leave in contact for 10min before rinsing; or salicylic acid 5% in 70% alcoholic solution; or fluconazole 400mg as a single dose.

Hypopigmentation due to tuberculoid leprosy is more chronic, and scale, if present, is more adherent and does not usually exfoliate easily. These patches will be anaesthetic on testing.

Vitiligo

Vitiligo is the most important cause of depigmentation (distinguish clinically from hypopigmentation; see Colour Plate 22e). Melanocyte death → patches of complete depigmentation, often in symmetrical distribution, occasionally → generalized. Hair may turn white. Affects ~2% of individuals, and can be very upsetting in those with pigmented skin, with fear of contagion and genetic transmission. There may be a personal or family history of autoimmune thyroid disease, pernicious anaemia, or diabetes. Treatment is largely ineffective; patients should avoid spending money on a search for cures. Camouflage with sweat- and waterproof creams is tedious to apply, but safe and effective.

Albinism

Caused by defects or absence in the enzyme tyrosinase, which is required for melanin synthesis → white skin and hair, and lack of iris pigmentation. Those affected develop potentially fatal squamous cell skin cancers in early adult life. Absent retinal pigment → ↓ vision, photosensitivity, and nystagmus which disturb schooling. In some communities, significant stigma is attached to the condition. In certain areas (e.g. Tanzania), special programmes exist to educate communities to manage those affected.

Box 13.6 Causes of hyperpigmentation

- Post-inflammatory hyperpigmentation.
- Addison's disease.
- Liver disease, e.g. porphyria cutanea tarda.
- Haemochromatosis.
- Acanthosis nigricans.
- Chloasma (melasma).
- Renal failure.
- Drugs, e.g. amiodarone, clofazimine.
- Naevi.
- Melanoma.
- Congenital, e.g. neurofibromatosis, Peutz–Jeghers syndrome.

Box 13.7 Causes of hypopigmentation

Congenital

- Albinism.
- Phenylketonuria.
- Tuberous sclerosis.

Acquired

- Post-inflammatory hypopigmentation (including onchocerciasis).
- Pityriasis alba.
- Pityriasis versicolor.
- Tuberculoid leprosy.
- Lichen sclerosus et atrophicus.
- Drugs (e.g. skin-lightening creams).

Causes of depigmentation

- Vitiligo.
- Albinism.

Skin cancers

Most important risk factor for skin malignancy is sun damage, either long term (most skin cancers) or sun burn (melanoma). Melanin protects against sun damage, so albinos and light-skinned individuals have ↑ cancer risk. Seek shade, use sunscreens on sun-exposed parts of body, and wear a hat outdoors. Infants should be protected from sunburn.

Actinic (solar) keratoses

These are premalignant, hyperkeratotic, adherent sandpaper-textured lesions on an erythematous base in adult light-skinned persons with long-term sun exposure. They may → squamous cell carcinoma (SCC). Persistent lesions should be destroyed by curettage, cryotherapy, or daily application of topical fluorouracil cream for 14d.

Squamous cell carcinoma

SCC occurs in sun-exposed areas. May develop from actinic keratoses or at edges of chronic ulcers and areas of inflammation (Marjolin's ulcer). Oral lesions occur in long-term smokers. Usually, a fleshy dry nodule breaks down to form an ulcerating lesion with hard raised edges. Systemic metastasis may occur, especially in albinos.

Management Early, radical, local excision.

Basal cell carcinoma (BCC)

Occurs predominantly in sun-exposed areas on the face. Usually slow-growing shiny papule with branched telangiectasia which may form a central ulcer with a rolled pearly edge. Usually slow-growing papule grows slowly or breaks centrally → ulcer with a rolled 'pearl-coloured' edge. Local infiltration may gradually → extensive tissue damage and disfigurement, but BCC does not metastasize.

Management Excision, curettage, cauterization, or cryotherapy. Fluorouracil cream or imiquimod cream may be used for superficial lesions or after surgery. Radiotherapy is also effective.

Melanoma

Any pigmented lesion that shows variable pigmentation, changes shape, thickness, or colour, starts to bleed, or ulcerates, should be considered a potential melanoma. Pigmented satellite lesions around a mole also suggest a melanoma. Melanoma is more common in people with many (>25) moles, who should be encouraged to examine these regularly (take pictures every 3mths with mobile phone) and report changes to a doctor. In Africans, melanoma commonly occurs on the soles (acral lentiginous melanoma) and may only be recognized following metastasis to lymph nodes or other sites. Original lesion may be innocuous.

Management Biopsy to confirm diagnosis. Referral to specialist centre for further management.

Common cutaneous viral infections

Herpes simplex

HSV-1 and HSV-2 cause mucocutaneous disease, keratitis, encephalitis, and aseptic meningitis. Transmission is by direct contact through mucosal surfaces (oral or genital) or skin abrasions. 1° mucocutaneous disease, including gingivostomatitis, pharyngitis, herpes labialis (cold sores), and genital herpes, may be due to either HSV subtype, but *recurrent* oral herpes is most commonly due to HSV-1 and recurrent genital herpes is caused by HSV-2. Recurrences are often precipitated by sun exposure, trauma, or fever.

After a few days of prodromal burning sensation, erythema appears → typically grouped vesicles within 24h. Fever, malaise, and lymphadenopathy are associated with 1° infection. A severe, potentially fatal form with widespread vesiculation particularly affecting face (eczema herpeticum) may occur in patients with atopic eczema and staphylococcal colonization. HSV may also trigger erythema multiforme.

Management Treat herpes labialis with zinc oxide ointment or zinc oxide and castor oil. Protect from sunlight. More severe infections: aciclovir (200–400mg 5× a day) or IV (5–10mg/kg tds) for 5–10d, or valaciclovir 500mg bd or famciclovir 250 tds for 5d, higher doses in the immunosuppressed. Frequent severe recurrences warrant oral aciclovir prophylaxis. In eczema herpeticum, add systemic antibiotics +/− topical steroids.

Varicella zoster virus

VZV causes chickenpox (varicella) following 1° infection, and shingles (herpes zoster) following reactivation of latent virus in sensory ganglia. Transmission is by respiratory droplet inhalation or contact with vesicular fluid.

Chickenpox is generally a mild in children (Box 13.8), but may be severe in neonates, adults (esp. in pregnancy), and the immunocompromised. Prodrome of fever, headache, and malaise. Rash is an itchy erythematous eruption involving the scalp and face and moving distally to involve trunk. Daily 'crops' of lesions progress from papules to vesicles, pustules, and scabs and all stages may be present at once.

Complications

2° *Staphylococcus aureus* and *Streptococcus pyogenes* infection is common in children and may → sepsis or skin scarring; pneumonitis (mainly seen in adults, especially smokers); mild encephalitis (ataxia); thrombocytopenia.

Herpes zoster usually occurs only once, often in the elderly or immunosuppressed. A few vesicles may occur outside the affected dermatome due to haematogenous spread. Paraesthesia and shooting pains in the affected dermatome may precede the vesicles, erythematous rash, and mild fever. Vesicles scab after 3–7d. Zoster (or zoster scars) in patients <40yrs old or in >1 dermatome suggests ↓ cell-mediated immunity, esp. HIV.

Complications include:

- *Post-herpetic neuralgia*: may be very painful and difficult to treat—amitriptyline (10–25mg nocte), carbamazepine (600–800mg od), gabapentin (300–900mg od to tds) or pregabalin (25–75mg od).

- *Herpes zoster ophthalmica (of the first division of the Vth cranial nerve)*: may be complicated by conjunctivitis, keratitis, and periorbital swelling.
- *HIV-associated herpes zoster*: delayed healing, multidermatomal zoster, dissemination, and complications are commoner.

Management

Antiviral therapy should be initiated within 72h of onset of the chickenpox or zoster and continued for 7d. Give aciclovir 800mg oral 5× daily or 10mg/kg IV tds in severe infections; alternatives are valaciclovir (1g oral tds) or famciclovir (500mg oral tds) for 1wk. Risk of zoster in the elderly ↓ by zoster vaccine given to adults aged >60yrs.

Box 13.8 Chickenpox in children

- Treat symptoms (paracetamol, topical antipruritics, e.g. calamine or phenol-zinc lotion). Low threshold for use of a broad-spectrum antibiotic (e.g. co-amoxiclav or flucloxacillin) esp. if any sign of local or systemic bacterial infection.
- *In neonates/high-risk groups*: aciclovir may ↓ duration and complications (oral: 200mg qds if age <2yrs; 20mg/kg (max. 800mg) qds if 2yrs. IV: 10–20mg/kg if age <3mths; 250mg/m² if 3mths–12yrs).

Common warts

Warts are caused by many strains of HPV, and affect ~10% of young people at any time. Wart may be nodular, flat, or occasionally filiform (long and slender, e.g. on eyelids). If on sole of foot (plantar wart, verruca), wart is usually painful because pressure forces lesion to form below level of epidermis, and layer of stratum corneum may partly obscure it. Warts of all types may be widespread and persistent in HIV.

Treatment Generally regress spontaneously in time; wart paints (e.g. topical salicylic acid 12–50%), curettage, cryotherapy. Pieces of lemon peel soaked in vinegar applied at night helpful for larger lesions where appropriate.

Poxvirus infections

Molluscum contagiosum

Molluscum contagiosum (➲ Colour plate 16) is caused by a poxvirus → 0.2–0.4cm smooth 'warts' with central umbilication. It is common in children, in whom spontaneous resolution is the rule. Widespread lesions may occur in HIV.

Treatment

Local application of, e.g. phenol or trichloroacetic acid spiked into the centre of the lesion; cryotherapy, curettage.

Monkeypox and tanapox

These poxviruses, closely related to smallpox, cause occasional infections after contact with a range of mammals. The rash (one or two lesions in tanapox; many covering the whole body in monkeypox) is preceded by a 2–3d prodromal period with fever and other systemic signs (Fig. 13.6). Lymphadenopathy occurs in monkeypox, characteristically involving both femoral and inguinal nodes. Unlike chickenpox, lesions are all at same stage and peripheries are involved early. Both infections tend to resolve without treatment. Outbreaks may occur with monkeypox.

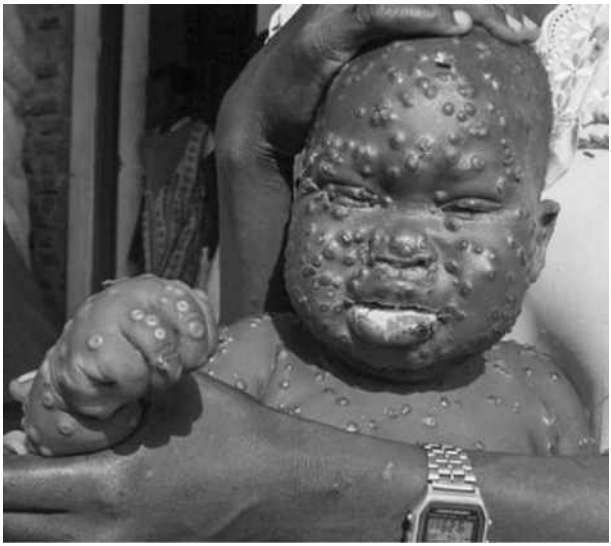

Fig. 13.6 A child in northern Kenya with monkeypox. In contrast to chickenpox, these vesicles are umbilicated, less fragile, larger, and occur both centrally and peripherally from the outset. The child made an uneventful recovery. Image courtesy of Médecins Sans Frontières.

Cutaneous leishmaniasis

A widespread disease, caused by several species of *Leishmania* manifesting in different ways depending on species and host response. *L. tropica* is anthroponotic; the *L. mexicana* and *L. braziliensis* species complexes (New World) and *L. major* (Old World) are zoonoses of rodents, dogs, or other mammals. Transmission of *Leishmania* promastigotes is by the bite of infected *Phlebotomus* and *Lutzomyia* sandfly vectors, following which the parasite multiplies in skin macrophages (Box 13.9; ➲ Visceral leishmaniasis (kala-azar), p. 732).

Clinical features

Weeks to months after a bite, a nodule develops at the bite site which grows slowly (up to 5cm), becomes ulcerated, and is covered by a crust which may drop off to expose a relatively painless ulcer—pain often indicates 2° bacterial infection. See Colour Plate 13. The ulcer may be dry or exudative, depending on the species. It heals over months to years, leaving a 'tissue paper' scar. Satellite lesions may occur. 2° infection is uncommon. *L. mexicana* classically causes lesions of the pinna ('chiclero ulcer') that take years to heal, often destroying the pinna.

Less common types

- Mucocutaneous leishmaniasis (MCL) 'Espundia' can occur in New World cutaneous leishmaniasis (CL) and rarely with other species. *L. braziliensis* is the most important cause (also occurs with *L. guyanensis*, *L. panamensis*). 2° mucocutaneous lesions develop in <5% of CL patients, usually months or years after 1° lesion has healed. Starting on the upper lip or nostril edge, untreated MCL slowly spreads destroys the mucosa and cartilage of the nasopharynx, larynx, or lips.
- Disseminated cutaneous leishmaniasis (DCL) is usually caused by *L. mexicana* or *L. aethiopica*: the 1° nodule spreads slowly without ulceration while 2° lesions appear symmetrically on limbs and face. Patients lack cell-mediated immunity, so vast numbers of parasites are found in lesions with minimal surrounding inflammatory reaction. Responds slowly to treatment, which may need to be prolonged to prevent relapse.
- Leishmaniasis recidivans is usually caused by *L. tropica*, often on the cheek. The lesion heals in the centre, but nodules with scanty parasites persist at the edges for years (Fig. 13.7).

Diagnosis

This is often clinical in resource-poor settings, supported by identification of Giemsa-stained parasites from microscopy and/or culture from skin smears taken from the edge of active ulcers. PCR, where available may ↑ sensitivity and allow diagnosis to species level. PCR is important in CL from the Americas, to determine whether there is a risk of later MCL.

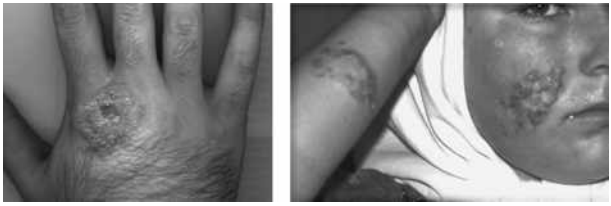

Fig. 13.7 Cutaneous leishmaniasis of the hand due to *L. tropica* (left) and leishmaniasis recidivans of the face and arm (right).

Box 13.9 Cutaneous leishmaniasis

Local treatments for Old World CL

Local treatments are suitable for Old World CL (*L. tropica* and *L. major*) and *L. mexicana* as there is no risk of these causing later MCL.

- Intralesional infiltration of sodium stibogluconate or meglumine antimoniate are widely used: 1mL of undiluted antimonial is injected into the base and edges of lesion. Repeat 2–3× weekly for 2–3wks. If very painful, can dilute with lidocaine 2%.
- *Leishmania* are killed at 40–42°C, so heating wound by radiofrequency or heat pads improves healing.
- Cryotherapy is successfully used in Old World CL, either alone or combined with intralesional antimonial.
- Topical treatment with paromomycin 15% ointment is effective in *L. major* and *L. mexicana*.

Systemic therapy for Old World CL

L. tropica and *L. major* only warrant systemic treatment if:

- Sores too large or badly sited for local therapy.
- Ulcerated or severely inflamed sores, or overlying a joint.
- Disease with lymphatic spread.
- Lesions with involvement of cartilage.

Treatments

- Oral fluconazole 200mg od for 6wks is effective in *L. major* CL.
- Miltefosine or injections of antimonials or amphotericin, see later in this box.

Systemic therapy for New World CL

CL from Central or South America could be caused by the *L. braziliensis* species complex. If in doubt, consider all New World CL to be *L. braziliensis*, because differentiation from *L. mexicana* is usually impossible geographically, clinically, or parasitologically unless PCR available. Systemic treatment of *L. braziliensis* CL should prevent subsequent MCL.

Treatments

- 10–20mg/kg/day sodium stibogluconate by IM or slow IV route, or meglumine antimoniate by deep IM for a minimum of 4wks, or until lesion healed.
- Pentamidine isetionate 4mg/kg 1–2 × weekly until lesion no longer visible. For *L. braziliensis guyanensis* 4 doses in 7d (every other day).
- Miltefosine 50mg bd for 28d is successful in many cases.
- MCL responds well to liposomal amphotericin at a dose of >2mg/kg for at least 20d (gives similar cure rates as and fewer adverse events than conventional amphotericin).

Treatment of diffuse CL

DCL is difficult to cure: prolonged courses of sodium stibogluconate, meglumine antimoniate, or miltefosine have been successful.

Lymphoedema (elephantiasis)

Lymphoedema is caused by obstruction to lymph flow → regional accumulation of lymph in the soft tissues. There is ↑ susceptibility to soft tissue infection → further lymphatic damage and a vicious cycle of worsening lymphoedema. In some conditions (particularly lymphatic filariasis (LF)), chronic trophic skin changes including hyperkeratosis, nodular fibrosis, and excess adiposity → elephantiasis of the affected limb or body part; see Colour Plate 18a.

Causes of lymphoedema include:

- LF (➲ Lymphatic filariasis, p. 572).
- Malignancy (including lymphatic involvement, radiotherapy, surgery).
- Chronic oedema (e.g. congestive cardiac failure).
- Lymphatic blockage due to TB, leprosy, or KS.
- Podoconiosis (distinguishable from LF by its upward ascendance from the foot whereas LF descends from upper leg/genitals). Podoconiosis is a cause of lymphoedema in certain highland areas of East and Central Africa rich in volcanic soils. It is often mistakenly diagnosed as LF. Microscopic mineral particles penetrate the dermis of the sole of foot and cause chronic lymphatic damage, especially in young adults who habitually walk barefoot. There may be a genetic predisposition.
- Congenital (Milroy's disease).

Management

Involves treating the underlying cause and general measures to promote lymph flow and prevent disease progression and complications (Box 13.10).

Box 13.10 General measures in management of lymphoedema

Promote lymph flow by ↓ gravitational venous load on the impaired lymphatics and preventing the cycle of inflammation and further lymphatic damage.

In patients with established severe lymphoedema/elephantiasis, collateral lymphatic channels can re-establish lymph flow if kept free from 2° infection. Prevention/treatment of infection ↓ social stigma associated with foul smelling, chronically infected tissues.

Minimize risk of further lymphatic damage due to inflammation

- Wash the affected part twice daily with soap and water.
- Use emollients (aqueous cream, vegetable oils, or white soft paraffin) to promote skin barrier function.
- Wear shoes; keep nails clean.
- Treat minor wounds or abrasions with topical antiseptics.
- Soak foot in potassium permanganate (1:10,000) solution.
- Early antibiotic treatment of soft tissue infections.
- Promote lymph flow in the affected limb.
- Exercise.
- Raise affected limb at night.
- Give diuretics to reduce venous load.
- Deep expiratory breathing, e.g. chanting (↑ venous return).
- Massage affected limb.
- Compression bandages, stockings, or laced boots.

Lymphatic filariasis

LF is caused by three geographically distinct (Fig. 13.8) species of filarial worm, *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori* (Fig. 13.9). The life cycle is shown in Fig. 13.10 (Colour Plate 18b).

Transmission occurs via the bite of mosquito vectors. Infective microfilariae enter host during a blood meal and migrate to lymphatics, particularly around groin and axillae, where they develop into adult worms, which may survive >10yrs. Females grow up to 10cm in length (males ~4cm) and produce microfilaria (~260μm), which enter the bloodstream. Onward transmission occurs when microfilaria are taken up by several species of mosquitoes during a blood meal. Host pathology is thought to be due to the immune response to adult worms and endosymbiotic *Wolbachia*. Microfilariae are responsible for tropical pulmonary eosinophilia (➲ Tropical pulmonary eosinophilia, p. 206). In endemic areas, asymptomatic microfilaraemia is common, as are asymptomatic seropositive patients without microfilaraemia.

Acute lymphatic filariasis ('filarial fever')

Usually recurrent, most commonly affects the limbs, spermatic cord/testes (funiculitis/epididymo-orchitis +/–hydrocoele), and breasts, and encompasses two syndromes:

- *Acute filarial lymphangitis (AFL)*: caused by death of adult worms → a local inflammatory nodule/lymphangitis which spreads distally, accompanied by systemic symptoms including fever, rigors, headache, myalgia, arthralgia +/– delirium.
- *Acute dermatolymphangioadenitis (ADLA)*: due to 2° bacterial infection → ascending lymphangitis with associated soft tissue infection/inflammation (cellulitis) and systemic upset. Lymphatic damage from recurrent attacks → chronic LF.

Chronic lymphatic filariasis

Usually occurs as a result of lymphatic damage from recurrent acute attacks, which continue to complicate and exacerbate chronic phase of disease. Clinical features include:

- Hydrocoele, which may be massive and interfere with walking.
- Lymphoedema (elephantiasis) of the legs is common, usually asymmetrical, and starts distally; see Colour Plate 18a.
- Chyluria and lymphuria are due to rupture into the renal pelvis or bladder of damaged lymphatics draining (1) intestines → fat in urine (chyluria) or (2) other organs → lymph in urine. Associated haematuria may cause clot retention. Chronic chyluria may cause malabsorption.

Other complications

Other complications attributed to LF, often in the absence of microfilaraemia, include arthritis (especially knee); endomyocardial fibrosis; skin rashes; thrombophlebitis; and nerve palsies.

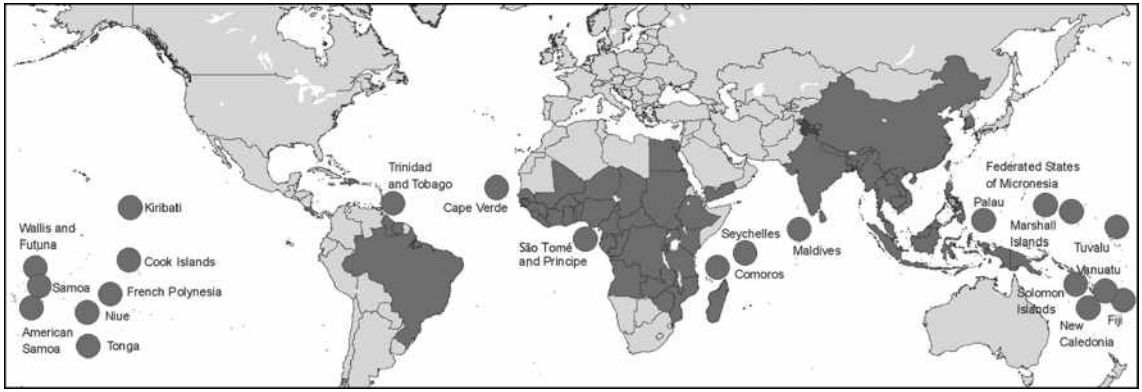

Fig. 13.8 Global distribution of lymphatic filariasis which affects 120 million people in 83 countries. Reproduced with permission from *Weekly epidemiological record*, No. 22, p. 224, Figure 2 © WHO 2006. All rights reserved.

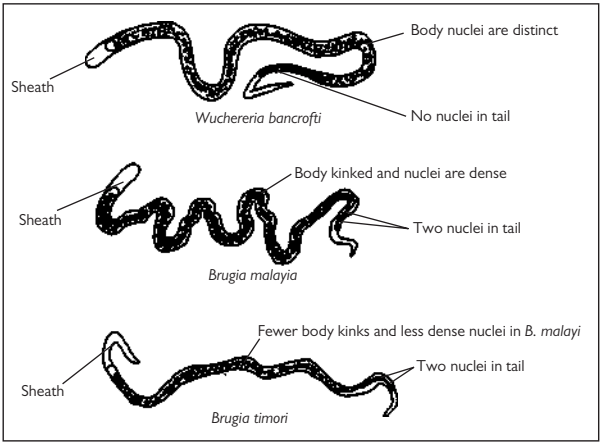

Fig. 13.9 Blood film appearances of the microfilariae lymphatic filariasis.

Microfilarial periodicity

Parasitaemia is periodic, peaking at key biting time of mosquito vector in a particular location. *W. bancrofti* and *B. malayi* usually exhibit nocturnal periodicity (peak parasitaemia around midnight); in the Pacific, *W. bancrofti* exhibits diurnal periodicity (peak about midday). Nocturnal and diurnal *subperiodic* forms also occur with less marked peaks of parasitaemia at night and day respectively.

Diagnosis

In endemic areas LF diagnosis is largely clinical and may be overdiagnosed. Parasitological diagnosis relies on isolation of microfilaria from blood; 10mL of blood should be taken during peak parasitaemia into citrated blood bottles (such as used for ESR or prothrombin time). See Table 13.3; Colour Plate 18b.

Detection methods

Polycarbonate membrane filtration: this technique is widely used and can detect very low parasitaemias.

- Nucleopore polycarbonate membranes, 25mm diameter, 5µm pore size, are held in a Millipore Swinnex™ filter holder, using a rubber gasket to secure the membrane.
- Draw up 10–20mL of 1:1 saline diluted blood into a 20mL syringe.
- Connect the syringe to the filter and gently push the blood through the filter membrane.
- Repeat until all of the blood has been filtered.
- Draw up 20mL of saline into the syringe, flush through the filter, repeat using air.
- Unscrew top of filter and use forceps to transfer to a slide.

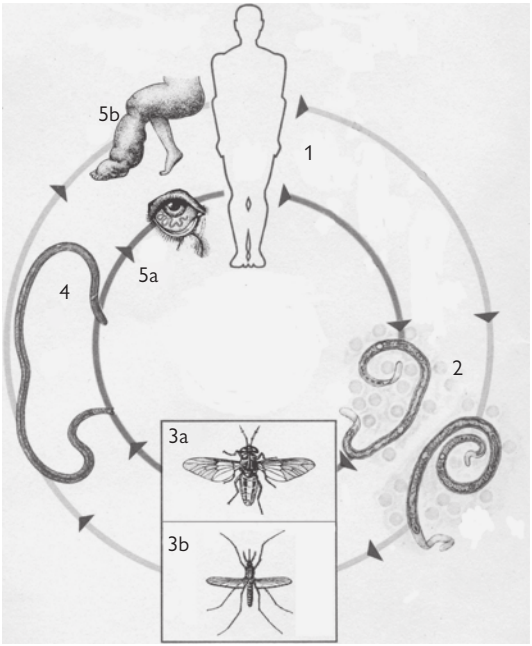

Fig. 13.10 Life cycles of lymphatic filariasis (outer circle) and loiasis (inner circle). Humans are the only host of sexually mature worms (5a, *Loa loa*, 5b *Wuchereria bancrofti*). Microfilariae (2) appear in the blood periodically—diurnally (loiasis) and nocturnally (lymphatic filariasis). Microfilariae are taken up during feeding by the intermediate host and vector: day-biting *Chrysops* flies (3a) or night-biting *Culex* mosquitoes (3b). In the vector, the microfilariae develop into infective metacyclic forms (4) which infect new human hosts when the vector takes a blood meal. Adapted from Piekarski, G *Medical parasitology in plates*, 1962, with kind permission of Bayer Pharmaceuticals.

- Add a drop of saline to the membrane and cover with a coverslip. Examine the membrane under the microscope, using a ×10 objective. Active microfilariae can be readily seen by their snake-like movement.

Saline/saponin method: add 8mL of 1% saponin in saline to 2mL of blood into a centrifuge tube.

- Mix by 15min to allow the blood to haemolyse.
- Centrifuge at 2000rpm for 15min to deposit the microfilariae.
- Discard the supernatant and use the deposit to make a wet preparation.
- Examine slide under ×10 objective; stain any microfilariae found and use a ×40 objective to note the arrangement of nuclei and presence of a sheath.

Simple card tests: to detect circulating filarial antigens are available for *W. bancrofti*, but not *Brugia* species.

Management

- Albendazole 400mg oral bd for 3wks kills adult worms, but is more effective in combination with diethylcarbamazine (DEC) or ivermectin.
- Albendazole 400mg plus either ivermectin 200 micrograms/kg or DEC 6mg/kg, as a single oral dose repeated annually for 5yrs, is now used for mass drug administration programmes (Box 13.11).
- Avoid DEC in *Onchocerca volvulus* and *Loa loa* endemic areas due to risk of Mazzotti reaction.
- Avoid DEC during acute attacks as macrofilaricidal activity +/– release of *Wolbachia* endotoxins (Box 13.12) may exacerbate symptoms.
- Ivermectin monotherapy only kills microfilaria so needs to be repeated during the lifetime of the adult worms (may be up to >10yrs).
- Doxycycline 100mg oral bd for 6wks (against *Wolbachia*) has been shown to reduce filaraemia and improve lymphoedema.
- Surgical management is required for chronic severe hydrocele. The long-term benefit of surgery for elephantiasis is often limited.
- For general principles of lymphoedema management, see ➲ Box 13.10, p. 571.

Box 13.11 Prevention and public health strategies

- *Prevention*: education to reduce vector–human contact; personal protection from mosquito bites; vector control.
- *Mass drug administration*: is promoted by GAELF (Global Alliance to Eliminate Lymphatic Filariasis) for communities with >5% infection prevalence. The whole community is treated once-yearly for 5yrs with single-dose albendazole 400mg plus either DEC 6mg/kg or ivermectin 200 micrograms/kg (avoid DEC in *Loa loa* or *O. volvulus* endemic areas). Addition of DEC to table salt has been used with success.

Table 13.3 Microfilarial periodicity and optimum times to detect microfilariae in blood

Species	Geographic location	Periodicity	Optimum collection time
Wuchereria bancrofti	Tropics/ subtropics	Nocturnal	Midnight
	Pacific	Diurnal subperiodic	16.00 hours
Brugia malayi	Southeast Asia and Southwest India	Nocturnal	Midnight
	Indonesia	Nocturnal subperiodic	21.00 hours
Brugia timori	Indonesia	Nocturnal	Midnight
Loa loa	West/Central Africa	Diurnal	13.00 hours
Mansonella perstans	Africa/South America	Non-periodic	Any time
Mansonella ozzardi	Central and South America	Non-periodic	Any time

Box 13.12 *Wolbachia* endosymbionts in human filarial infections

Endosymbiotic *Wolbachia* bacteria (related to *Rickettsia*) live within the adult filarial worms causing LF and onchocerciasis, but not *Loa loa*. *Wolbachia* are now recognized to be important in worm reproduction, development, and pathology. Release from adult worms of *Wolbachia* endotoxins is thought to play a major role in the inflammatory pathology of LF and onchocerciasis. Trials of anti-*Wolbachia* chemotherapy with doxycycline have shown significant benefits in both LF and onchocerciasis.

Wolbachia are not present in *Loa loa* and *Mansonella perstans*.

Onchocerciasis ('river blindness')

Onchocerca volvulus occurs in areas with fast-flowing rivers and biting *Similium* blackflies, the parasite's vector. In W African savannah, it was a common cause of blindness until the Onchocerciasis Control Programme ↓ prevalence. Still causes blindness and skin manifestations in some areas.

Clinical features

- Subcutaneous nodules containing adult worms, conspicuous over bony prominences (e.g. iliac crests, ribs, knees, trochanters).
- Cutaneous and eye manifestations due to host inflammatory reactions to dying microfilariae which migrate in the skin (Box 13.13) and eye.
- Ocular lesions include transient punctate keratitis and potentially blinding conditions (e.g. sclerosing keratitis, iridocyclitis, optic atrophy).

Diagnosis

Confirmed by finding microfilariae in skin snips or the eye. Ask the patient to put their head between their knees for >2min before examining the anterior chamber with a slit-lamp. If skin snip and eye examinations are both –ve, but onchocerciasis is still strongly suspected, perform the Mazzotti test: give DEC 50mg oral; ↑ pruritus within 24–48h indicates that the patient is infected (Box 13.14, p. 579).

Management

- One dose of oral ivermectin 150 micrograms/kg clears microfilariae from skin for several months. Repeat the dose when patient is symptomatic (typically each 6–12mths) throughout lifespan of adult worms (15–20yrs).
- Doxycycline 100mg oral bd for 4–6wks (against *Wolbachia* endosymbionts) ↓ or eliminates microfilariae in skin for 12–18mths and ↓ the number of adult worms.

Prevention Ivermectin mass distribution programmes; vector control.

Box 13.13 Forms of dermal onchocerciasis

- *Acute papular onchodermatitis*: small scattered itchy papules, +/– vesicles and pustules, +/– skin oedema, trunk and upper limbs.
- *Chronic papular onchodermatitis*: larger itchy, hyperpigmented, often flat-topped papules +/– hyperpigmentation.
- Lichenified *onchodermatitis*: intensely itchy, hyperpigmented papulonodules or plaques, often on the legs, which become confluent; Colour Plate 18c.
- *Atrophy*: loss of elasticity with excessive wrinkles particularly on buttocks; inguinal skin forms hanging groins, often filled with enlarged lymph nodes.
- *Depigmentation (leopard skin)*: patches of hypo- or depigmentation contrasted with normally pigmented skin around hair follicles.

Box 13.14 Mazzotti reaction

DEC may → severe adverse reactions in *O. voluvulus* infection due to an immune reaction to worm death. Local reactions include skin rashes, exacerbation of eye lesions; severe systemic reactions may occur with fever, myalgia, arthralgia, respiratory distress, and shock.

Avoid DEC therapy in onchocerciasis endemic areas.

Loiasis (*Loa loa*)

Loa loa nematodes are transmitted in Central African rainforests by bites of *Chrysops* horse flies. As injected filarial larvae mature, they migrate away from sites in the subcutaneous layers (producing itching, prickly sensations) or deeper fascial layers (pain, paraesthesia). Transient migratory angio-oedema, 'calabar swellings' of limbs, occur at intervals lasting a few hours to days, due to a host immune response to migrating adult worms; overlying skin is slightly inflamed (Fig. 13.11). Worms migrating beneath conjunctiva may be clearly visible for minutes to hours, and produce acute eye irritation.

Diagnosis Clinical or serological; microfilariae can also be found in filtered blood samples collected around midday (Fig. 13.12).

Management

Oral DEC 1mg/kg on day 1; 1mg/kg bd on day 2; 2mg/kg bd on day 3; and 2–3mg/kg tds from day 4–21. Start people with heavy microfilaraemia at a low dose and give steroid cover for first 2–3d (risk of meningoencephalitis with dying microfilaria). Check for mixed infection with *O. volvulus* before using DEC—if present, pre-treat with ivermectin 150 micrograms/kg oral stat as there is risk of Mazzotti reaction (➲ Box 13.14, p. 579).

Prevention Avoid vector contact; DEC 300mg oral once weekly may provide effective prophylaxis; vector control.

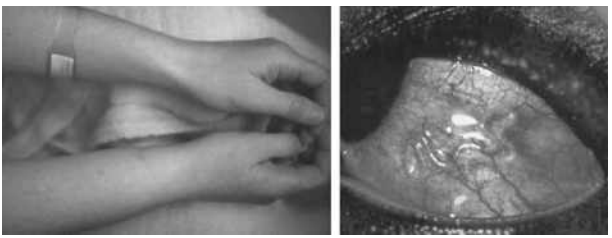

Fig. 13.11 *Loa loa*: calabar swelling (left): this patient noted an uncomfortable swelling in his right forearm, which moved up his arm over 3–4d and then disappeared. A subconjunctival adult worm (right) of *Loa loa* is seen: this patient felt irritation in his eye and, when looking in the mirror, noted a mobile thread-like worm crossing the eye under his conjunctiva; it disappeared in about 1h.

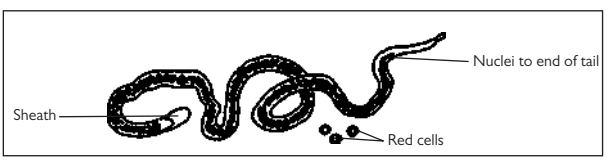

Fig. 13.12 Appearance of *Loa loa* microfilaria on a blood film.

Dracunculiasis (Guinea worm)

Dracunculus medinensis infection follows ingestion of water containing its copepod crustacean vector (➲ Colour plate 17). Released larvae migrate into body cavities, mature, and mate. Months later, adult females (50–100cm long) migrate subcutaneously to extremities, where an ulcer forms and the tip of the worm protrudes. In contact with water, the uterus of a larvae worm prolapses through the skin surface to release larvae.

Clinical features

Include systemic hypersensitivity. Protrusion of the gravid female causes a painful blister, which may become 2° infected with bacteria. Some worms migrate to sites such as brain, joints, or eyes, resulting in cerebral/subdural abscesses, arthritis, or blindness. Diagnosis is clinical in endemic areas in sub-Saharan Africa.

Management

Remove female worms before they blister by identifying them subcutaneously, making a small incision in the skin at their midpoint, and pulling the worm out with careful traction and massage along its track. Metronidazole 400mg tds oral for 1wk reduces inflammation and eases the removal. After a blister has burst, analgesics will be needed before the worm can be pulled out. Keep the blister clean and covered.

Prevention

Improve water supply or filter drinking water through cloth to remove crustaceans. The Guinea worm eradication programme has ↓↓ transmission to scattered foci within affected countries.

Other parasites that invade the skin

Cutaneous (furunculoid) myiasis

This is an infestation of the skin with fly larvae (maggots). *Dermatobia hominis* (the tropical botfly) is endemic in Central and South America. Female flies attach eggs to mosquitoes and other blood-sucking arthropods, which deposit eggs during a blood meal. Warmth from host causes eggs to hatch and larvae penetrate host skin (Fig. 13.13). In sub-Saharan Africa, female *Cordylobia anthropophaga* (tumbu) flies lay their eggs in shaded soil or clothing hung out to dry (particularly if contaminated by urine); larvae hatch in 2d and penetrate skin. In both cases, as each larva grows subcutaneously, a 'boil'-like lesion with central punctum develops.

Management Removal of the larvae. Occluding punctum with petroleum jelly or fat may allow larva to be grasped as it emerges for O_2. Surgical removal is sometimes required. Treat any 2° bacterial infection.

Prevention Insect repellents, clothing, and mosquito nets for *D. hominis*; ironing clothing (including underwear) destroys the eggs of *C. anthropophaga*.

Tungiasis (*Tunga penetrans*, the jigger flea)

The 1mm female pig flea burrows into the skin, usually of the toe webspaces, and grows to about 1cm in 2wks. The female discharges its eggs on the surface and its collapsed carcass is extruded.

Management Careful removal of flea and eggs. Avoid 2° bacterial infection.

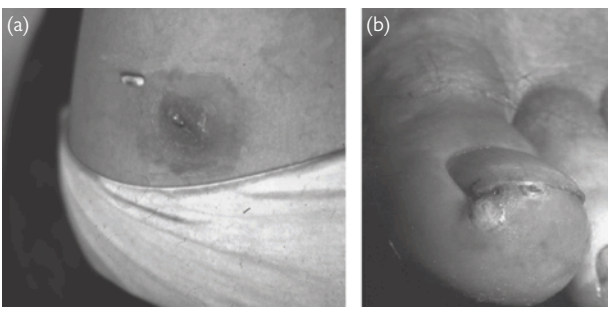

Fig. 13.13 (a) Furunculoid myiasis: this traveller developed a 'boil' on her buttock soon after return from Africa from which the larva of *Cordylobia anthropophaga* (the 'tumbu fly') was extracted. (b) *Tunga penetrans* (the 'jigger flea'): two lesions are seen at the edge of the toenail.

Cutaneous larva migrans

Infection with filariform larvae of dog and cat hookworms (*Ancylostoma caninum* or *A. braziliense*) for whom humans are accidental hosts (➔ Colour plate 14). Larvae migrate 1–2cm per day in the skin, leaving an intensely itchy, red irregular track, before they eventually die.

Management Single-dose ivermectin 200 micrograms/kg (12mg average adult dose) or albendazole 400mg oral. Thiabendazole 15% cream or 10–15% suspension can also be applied topically. Untreated, the rash will eventually resolve spontaneously.

Larva currens

A cutaneous eruption resulting from autoinfection into the skin (often of the buttocks/perianal area) by *Strongyloides stercoralis* (➔ Diarrhoeal diseases, p. 256). The urticarial wheals are linear and move ~1–2cm/h; the abdomen and buttocks are most affected (➔ Colour plate 15).

Non-venereal treponematoses

These disfiguring conditions primarily affect children in communities with poor hygiene. Like syphilis, they have three stages, with a long period of latency before the manifestation of 3° disease. Unlike syphilis, the 3° lesions are infective, causing problems for eradication, since it is difficult to identify latent carriers. Transmission is by direct contact; probably through abrasions (spirochaetes cannot penetrate intact skin; see Table 13.4).

Clinical features

Yaws

1° lesion is a papule, → round/oval 2–5cm painless, itchy papilloma. It normally heals in 3–6mths. Weeks to years after this lesion resolves, multiple 2° lesions occur in crops on any part of body and last up to 6mths. They are papules or raspberry-like lesions of various shapes; they may ulcerate and form yellow-brown scabs. Other lesions include dermatitis or hyperkeratosis of palms and soles; local lymphadenopathy; dactylitis; long bone swelling; rarely, osteitis of nasal bones. After a latent period, disease reappears with necrotic destruction of skin and bones (gummas). Other clinical features include hyperkeratosis; palatal destruction and 2° infection; saber tibia; bursitis.

Endemic syphilis (bejel)

1° lesion is rarely seen. First lesions are usually painless ulcers of lips and oropharynx. Osteoperiostitis of long bones, condylomata lata, angular stomatitis; rarely a 2° syphilis-like rash; and generalized lymphadenopathy. Late lesions include bone destruction (as in yaws), skin ulcers, and palmar and plantar keratosis.

Pinta

Pinta primarily affects the skin. Satellite lesions surround 1° papule; there is regional painless lymphadenopathy. 2° stage plaques appear within a few months anywhere on the body. 3° disease involves depigmentation and atrophy of the skin.

Diagnosis

Motile spirochaetes can be seen on dark-field microscopy of lesion exudates. There are no serological or morphological features that differentiate syphilis-causing *Treponema pallidum* from the other treponemes. The precise diagnosis is clinical.

Management

A single dose of benzathine benzylpenicillin 0.9g IM (alternatives: erythromycin 250–500mg oral qds or amoxicillin 500mg tds for 15d).

Prevention

Community mass treatment with a single dose of 30mg/kg azithromycin is a highly effective WHO strategy for elimination of yaws, combined with trachoma control. An alternative approach is identification of active cases, followed by treatment of all contacts. If >10% in community are actively infected, all should receive treatment with penicillin or azithromycin.

Table 13.4 Non-venereal treponematoses

	Yaws	Bejel	Pinta
Organism	*T. pertenue*	*T. pallidum*	*T. carateum*
Age group (yrs)	15–40	2–10	10–30
Occurrence	Africa	Africa	Latin America
	South America	Middle East	
	Oceania	Asia	
Climate	Warm, humid	Dry, arid	Warm

Bone, joint, and soft tissue infections

Matthew Scarborough

Infections of skin

Skin infections can be divided into:
- *Pyodermas*: localized infections with pus formation within the skin.
- *Spreading infections*: diffuse infection spreading along tissue planes.

Pyodermas

Impetigo

Superficial infection of the epidermis, often at sites of skin damage (e.g. cuts, eczema, chickenpox, scabies, insect bites; Box 14.1). A golden-yellow vesicle quickly bursts → an area of epidermal loss → crusts over and enlarges; see Colour Plate 22d. There may be a little pus under the edges of the lesion. Impetigo is highly contagious: the 1° lesion expands to form satellite lesions and can be spread (usually on patient's own fingers) to elsewhere on the skin and to contacts. The most common pathogens are *Staphylococcus aureus* and/or β-haemolytic streptococci (BHS; e.g. group A BHS, also known as *S. pyogenes*).

Management
- Topical agents (e.g. mupirocin) if mild.
- Systemic antibiotics if more extensive or failed topical therapy (Table 14.1).
- Soak off crusts in saline or weak antiseptic.
- Wash skin daily with soap and water.
- Encourage hand hygiene and contact precautions.

Furuncles (boils), carbuncles, and abscesses

S. aureus causes abscesses in the dermis or subcutaneous fat. A furuncle (boil, pimple) is pus collecting in a hair follicle or a sebaceous/sweat gland in the skin. Carbuncles are furuncles that have spread deeper (often 2° to patient squeezing or sitting on the furuncle), so that multiple points of pus occur. An abscess is a collection of pus at an even deeper level; usually indicated by swelling, erythema, warmth, and fluctuance. Tenderness is common in all skin infections, but pressure on an abscess is very painful.

Management
- Furuncles can often be managed with the application of warm compresses to promote spontaneous discharge.
- Drain pus and remove necrotic tissue and debris. Abscess cavity should be left to heal by 2° intention—do not suture.
- Drainage and good wound care alone may suffice but, if the infection spreads to the surrounding soft tissues, give systemic antibiotics (Table 14.1).

Spreading infections

These are more commonly caused by BHS than by *S. aureus;* other organisms account for a minority of cases.

Erysipelas

Acute, spreading infection in the epidermis, classically on the face but also commonly involving the legs. The affected skin becomes red, shiny, and tender, and the patient is often unwell and febrile. The involved area is sharply demarcated from normal skin because the dermal–epidermal

junction limits the spread of the inflammatory response. Severe infection → skin blistering; necrotic tissue ↑ toxin production so the infection becomes worse if the infection is not treated.

Management Antibiotics (Table 14.1).

Cellulitis

Acute infection involving the dermis and subcutaneous fat. There is usually diffuse swelling and the erythema is less clearly demarcated than in erysipelas. It commonly involves the lower leg, spreading from skin breaks such as minor injuries, fungal infection (e.g. athlete's foot), insect bites, or scabies. There may be underlying abscess formation, esp. in the hand. When cellulitis is near the knee or elbow but spares the extremity, consider an underlying prepatellar, pretibial, or olecranon bursitis.

Scaling/desquamation are normal after some days of infection; blisters protect the lesion and should be left intact unless they contain pus.

Management Antibiotics (Table 14.1), rest, and elevation.

Recurrence is relatively common. If multiple recurrences, consider:

- Prolonged treatment courses.
- Prophylaxis (phenoxymethylpenicillin 250mg bd or erythromycin 500mg od).
- *S. aureus* decolonization (e.g. 1wk doxycycline 100mg bd po + rifampicin 300mg bd po + daily 4% chlorhexidine shower + topical mupirocin ointment applied bd to nostrils and under fingernails).
- Standby antibiotics to take at the onset of symptoms.

Necrotizing fasciitis

Necrotizing fasciitis is a surgical emergency with high mortality. The most common cause is group A BHS, but it may involve other organisms (incl. anaerobes) and may be polymicrobial.

Infection spreads very rapidly in the loose connective tissue adjacent to the fascial plane → necrosis of subcutaneous tissues and thrombosis of blood vessels that supply the skin or muscle. Infection in deep tissues spreads very fast, but skin necrosis occurs relatively slowly; hence a relatively healthy appearance of the skin is deceptive. Look carefully for what looks like a faint but rapidly expanding bruise, and for pain that is disproportionate to the local physical signs. At surgery, deeper tissues may be extensively necrotic (do not bleed when incised); consequently, the patient usually has severe systemic upset, often with high fever and shock.

Diagnosis Largely clinical and surgical exploration essential to confirm or rule out the diagnosis. Development of fixed tissue staining, ecchymoses, crepitus, or superficial blistering early in disease (not late as in cellulitis) makes the diagnosis probable. Imaging (CT or MRI) may confirm the diagnosis in difficult cases but should never delay surgical exploration.

Management

- *Early surgery is mandatory*: explore the fascial plane and excise the affected area back to healthy, bleeding tissue. Repeated surgery is often necessary.
- Broad-spectrum IV antibiotics: co-amoxiclav plus gentamicin is a good first choice. If available, add clindamycin (antitoxin effect). Duration of

treatment should be guided by clinical response. Adjust antibiotics when cultures are available from surgical samples.
- Intensive care support and reconstructive surgery: without these, prognosis is poor.

Box 14.1 Soft tissue infections

Poverty, malnutrition, and ↓ access to antibiotics → a high incidence of severe soft tissue infections in the tropics. Some conditions, e.g. pyomyositis (➲ Pyomyositis, p. 592), are much more common in the tropics than in temperate zones.

Table 14.1 Common causative organisms and empiric antibiotic regimens

Condition	Microbiology	Treatment choices	Duration
Superficial infections			
Impetigo Furuncles Abscesses Carbuncles Erysipelas Cellulitis Bursitis	Group A BHS *S. aureus* (incl. MRSA*) Groups B/C/G BHS	1st: flucloxacillin or co-amoxiclav 2nd: clindamycin 3rd: clarithromycin 4th: co-trimoxazole	Until clinical resolution, usually 5–14d
Deep infections			
Acute native septic arthritis Acute osteomyelitis Pyomyositis Septic tenosynovitis Necrotizing fasciitis	*S. aureus* (incl. MRSA*) Group A BHS Mixed infection See text	1st: co-amoxiclav 2nd: ceftriaxone 3rd: ciprofloxacin + clindamycin 4th: Co-amoxiclav + gentamicin + clindamycin	See individual sections

* If MRSA suspected or proven add vancomycin (see also Box 14.2).

Bursitis

Bursitis most commonly involves the elbow or the knee, and presents as cellulitis over the joint, or as a red painful swelling. The pathogens are usually BHS or *S. aureus*. Although bursitis often restricts the movement of the joint, this is related to the mechanical effects of the swelling and the associated tenderness of the soft tissues; careful examination can usually distinguish bursitis from the much more serious condition of septic arthritis.

Management

- Antibiotics for 2–3wks (Table 14.1).
- Needle aspiration to remove pus for diagnosis and symptom relief.
- Avoid incision and drainage where possible: continued synovial fluid production produces high-volume wound drainage, can delay healing, and may sometimes → a synovial fistula.

In chronic bursitis, suspect TB, underlying osteomyelitis (erosion of bone on X-ray), or chronic septic arthritis.

Box 14.2 Methicillin-resistant *S. aureus* (MRSA)

Methicillin resistance occurs in clones of *S. aureus* due to mutation of penicillin binding proteins on their surface.

Methicillin resistance → resistance to all β-lactam antibiotics, including flucloxacillin, co-amoxiclav, and ceftriaxone.

MRSA is ↑ common in resource-poor countries, esp. in large urban centres. While β-lactams remain appropriate first-line empiric treatment for bone, joint, and soft tissue infections in most settings, always consider MRSA if poor clinical response.

It is important to establish local MRSA rates to guide empiric treatment regimens. In settings with high MRSA prevalence, empiric treatment for *S. aureus* infections should include MRSA cover.

Antibiotic treatment options

- *IV*: vancomycin, teicoplanin, linezolid.
- *Oral*: in most areas, doxycycline has high activity against MRSA, and in many areas, chloramphenicol, clindamycin, co-trimoxazole, and fusidic acid are effective. Rifampicin, although effective against most MRSA strains, must never be used as monotherapy and should generally be restricted for use in TB.

Prevention

- Infection control precautions (gowns, gloves, isolation/cohorting) can be used to ↓ transmission between patients in hospital.

Infections of muscle

Pyomyositis

Also called 'tropical myositis', this is a 1° bacterial infection of skeletal muscle that is common throughout the tropics and subtropics, esp. in young men.

There are three characteristic phases:

- *Invasive phase*: affected muscle is painful, hard, and woody on palpation. Patient may have little systemic illness; this phase may last for days–months. It is difficult to diagnose, and can sometimes be mistaken for a tumour.
- *Suppurative phase*: tissue liquefies → IM abscess and very tender swollen muscle. USS shows IM collections; for psoas abscess, may need CT or MRI. (*Note*: psoas abscess is also a complication of lumbar spinal infections and may not represent 'pure' pyomyositis.) Gram stain and culture of aspirated pus usually reveals *Staphylococcus aureus* (rarely BHS).
- *Systemic phase*: sepsis, bacteraemia, and metastatic infection may occur.

Management

- Drain abscesses surgically or percutaneously for source control.
- Antibiotics (➲ Table 14.1, p. 590). Duration of therapy usually 10–21d depending on adequacy of drainage and clinical response.

The overall prognosis is generally good.

Gas gangrene (clostridial myonecrosis)

A rapidly progressive, life-threatening, necrotizing infection within muscle, characterized by severe systemic illness, muscle pain, and muscle crepitus due to gas formation. Gas gangrene is generally caused by *Clostridium perfringens*, which produces toxins that cause muscle necrosis. The infection is acquired through environmental (particularly soil) contamination of deep wounds involving muscle.

Management

- Without successful treatment, the systemic effect of toxins is invariably fatal.
- Emergency surgical exploration and debridement of dead tissue is essential, often requiring excision of massive areas of muscle (for trunk wounds) and early amputation (for limb infection).
- Antibiotic therapy with high-dose penicillin (plus clindamycin if available) is important, but unlikely to be effective without surgery.

Prevention Good wound care/wound debridement.

Box 14.3 Septic tenosynovitis

Infections of the tendon sheath occur mainly in the hand or foot, and are usually due to trauma or spread of infection from joints or soft tissue. Haematogenous infection may also occur.

The likely infectious aetiology depends on the cause. Acute infection 2° to trauma or contiguous soft tissue infection is usually due to *S. aureus* or BHS, though a range of organisms may be implicated (e.g. if chronic ulceration).

Rarer causes of septic tenosynovitis in the non-traumatized hand incl. atypical mycobacteria (e.g. *Mycobacterium marinum*, *M. chelonae*, and *M. kansasii*); and environmental fungi such as *Sporothrix schenckii*; disseminated gonococcal infection; and *M. tuberculosis*.

Clinical features Pain and swelling of one or more fingers or the palm or dorsum of the hand. Swelling in the foot may be minimal if fluid drains via an ulcer.

Diagnosis Usually clinical, confirmed by surgery, USS, or MRI.

Management

- *Generally requires drainage of affected tendon sheath* to control the infection; determine the aetiology (send surgical samples for culture including mycobacterial and fungal culture if available) and to prevent adhesions and long-term stiffness.
- Soft tissue cover is important as tendons heal slowly if exposed.
- Antibiotics: treat pyogenic infections for 2–4wks (Table 14.1, p. 590). For mycobacterial or fungal infections, use standard courses for the pathogen.

Septic arthritis

Bacteria reach the joint by haematogenous spread or direct inoculation (trauma, ulceration, or iatrogenic). Bacterial multiplication in the joint → acute inflammation → destruction of articular cartilage and resorption of exposed bone → deformity, chronic osteomyelitis, and joint fusion. Bacteraemia and septicaemia may occur. If pus tracks and discharges externally, a sinus is formed.

Clinical features

Although most cases of acute or chronic infection involve a single joint, multiple joints are involved in 5–10% (Box 14.4).

- *Acute septic arthritis*: fever, pain, and loss of function. The joint is highly irritable; the patient resists both active and passive movement. Usually, the joint is obviously swollen, warm, and tender to touch, with little or no erythema unless accompanied by bursitis or cellulitis (Box 14.5).
- *Chronic septic arthritis*: swollen and painful joint, but little systemic illness. There may be obvious deformity or crepitus from gross joint destruction (Box 14.6).

Complications

Without timely and effective treatment → joint destruction. There may be osteomyelitis, septicaemia, and, in young children, growth plate disturbances → deformity or ↓ limb length. Complications are much more likely if treatment is delayed.

Diagnosis

- *Blood tests* may demonstrate inflammation, but lack specificity.
- *Synovial fluid aspiration* is essential: microscopy shows neutrophils and Gram stain may show bacteria; presence of crystals suggests gout or pseudogout as the cause (rarely crystal arthropathy can also be complicated by septic arthritis). Cultures are often +ve if sample taken before antibiotics.
- *Blood cultures* are frequently +ve so should be taken in all cases of suspected septic arthritis, ideally before antibiotics.
- *Radiology*: plain X-rays may show extent of joint damage, but changes only seen if infection present for more than ~10 days. CT and MRI reveal better the extent of bone and soft tissue infection, but radiological appearances take time to evolve and (esp. MRI changes) persist long after the infection is cured.

Management

- *Drainage of the joint* should be performed urgently by aspiration (repeated aspiration frequently required); arthroscopic washout; or open drainage. Consider open surgical drainage in particular for hip joints, when repeated drainage has failed, and for chronic septic arthritis.
- *Antibiotic therapy* (➲ Table 14.1, p. 590) is guided by Gram stain and culture results. Treat for at least 3wks—ideally IV for ≥1–2wks depending on adequate source control and clinical response. In joints with extensive pre-existing arthritis and exposed bone, or in compromised hosts (e.g. RA), treat for longer. 7d of treatment is usually adequate for gonococcal arthritis.

Box 14.4 Pathophysiology of bone and joint infections

- Soft tissue infections can spread contiguously or seed via the bloodstream → septic arthritis and acute osteomyelitis.
- If ineffectively treated, acute conditions → chronic, with bone and soft tissue necrosis usually requiring surgery.
- Common causes include injuries due to road traffic accidents, occupational accidents, armed conflict, and landmine injuries.
- Other important 1° infections of bone and joints are commoner in the tropics, e.g. TB, brucellosis, melioidosis, histoplasmosis, and blastomycosis.

Box 14.5 Organisms causing acute septic arthritis

- *S. aureus*: most common cause in all age groups and all countries. First choice—IV flucloxacillin (vancomycin for MRSA).
- *Haemophilus influenzae*: in populations without access to Hib vaccine. First choice in serious infections—ceftriaxone.
- *Beta-haemolytic streptococci*: group A, C, and G in all hosts; group B streptococcal infections more common in pregnancy, neonates, and diabetics. First choice—penicillin.
- *Enterobacteriaceae (e.g. Escherichia coli)*: more common in neonates and elderly. First choice—co-amoxiclav (or ceftriaxone).
- *Neisseria gonorrhoeae*: in sexually active individuals. First choice—ceftriaxone +/− azithromycin depending on local resistance profiles.

Box 14.6 Organisms causing chronic septic arthritis

The same organisms as acute septic arthritis, plus:

- *M. tuberculosis*.
- *Brucella*.
- Less commonly, fungi (e.g. *Candida*, *Sporothrix schenckii*).

Osteomyelitis

Infection of the bone → progressive bone destruction and sequestrum (dead bone) formation. Caused by haematogenous or contiguous spread of microorganisms or by direct inoculation. Organisms causing acute osteomyelitis are largely the same as those causing acute septic arthritis.

Clinical features

- *Acute osteomyelitis*: fever, localized bone pain, and loss of limb function. May → septic arthritis, esp. in young children.
- *Chronic osteomyelitis*: clinical features include chronic pain, acute flares of associated soft tissue infection, trophic skin changes +/− sinus formation (may discharge pus and/or gritty bits of dead bone), ↓ function, and/or chronic ill health. Visible or palpable bone in a wound makes osteomyelitis highly likely. An orthopaedic implant or an open fracture with a chronically draining wound is almost certainly infected.

Diagnosis

- *Blood tests*: WBC and CRP may be normal; anaemia is common in chronic infection.
- *X-rays*: become abnormal after ~10d with areas of demineralized bone (lytic areas), attempts to heal (periosteal reaction), and dead bone (sclerotic areas). Changes evolve over weeks to months. ↑ lucency around metalware suggests loosening (e.g. due to infection).
- *Other imaging*: USS can show abscesses adjacent to bone and delineates sinus tracts. CT is useful for assessing bony union, bone destruction and sequestrum. MRI detects marrow oedema, cortical breaches, sinus tracts, and soft tissue collections, but is less useful in patients with extensive metalware or recent surgery.
- *Cultures*: blood cultures are frequently +ve in acute osteomyelitis. Bone biopsy obtained radiologically or surgically (ideally before antibiotics), is more sensitive. Sinus tract swabs are of dubious value unless they grow *Staphylococcus aureus*.

Management

Aim to eradicate symptoms and restore/preserve function. Options include:

Control of intermittent flares with short courses of antibiotics Especially if symptoms mild, flares are infrequent and respond to antibiotics. Monitor for progression of bone involvement.

Suppression with long-term antibiotics If surgery impossible (e.g. for technical reasons or unaffordable) or likely to be worse than disease. Long-term antibiotics can → drying of sinuses, ↑ general health, and ↓ pain. Many patients can live with their bone infection for long periods; in some situations, this may be the best that can be achieved.

Eradication of infection Usually requires combination of thorough surgical debridement of all dead tissue, removal of foreign material (if present), and antibiotic therapy. Surgical success depends on adequate stabilization of the skeleton, careful management of dead space (defects in debrided bone are filled with muscle flap, cancellous bone graft, or antibiotic carrier) and adequate soft tissue cover. Antibiotic success depends on appropriate choice (informed primarily by susceptibilities of the pathogens), dose (sufficient to ensure adequate levels at the site of infection), and duration of therapy. The latter is poorly defined but is commonly 6–12wks for native bone infection and 3–6mths for prosthetic material-associated infection. Oral antibiotics with good bioavailability are as effective as parenteral antibiotics. Addition of antibiotics to acrylic bone cement or dead space filler generate very high local levels and may allow shorter courses of systemic therapy.

With expert surgery, >90% of cases can be arrested. However, even without surgery or antibiotics, spontaneous long-term arrest can occur if sequestra discharge spontaneously.

Box 14.7 Spinal infections

Common causes are *S. aureus*, *Brucella* spp., and TB. Initial blood-borne seeding to disc space → involvement of adjacent vertebral bodies. Paraspinal muscles may also become involved, with collections (e.g. psoas abscesses). Retropulsion of disc and inflammatory tissue, or spinal epidural abscess, may compress the spinal cord → paralysis.

Clinical features

Severe back pain, esp. at night; sudden paraparesis on a background of back pain and/or fever.

Diagnosis

Plain X-rays may show irregularity and destruction of end-plates adjoining the infected disc space. MRI provides the best imaging. If possible, aspirate paraspinal abscesses or biopsy the disc for culture to determine aetiology. Consider CXR +/− sputum examination for TB.

Management

- Antibiotics (➲ Table 14.1, p. 590). Treat pyogenic infections of the spine for 6–12wks depending on clinical and radiological response.
- Surgery is reserved for cases with acute spinal epidural abscess, persistent pain, mechanical instability, recurrent infection with abscess formation, or cord compression.
- Steroid therapy may be useful as an adjunct to ↓ oedema in spinal TB with significant neurological involvement.
- Patients with spinal TB infection may recover neurologically on anti-TB medication, even if presenting with paralysis.

The diabetic foot

The ↑↑ worldwide in T2DM → ↑ patients with diabetic foot complications. These arise from diabetic peripheral neuropathy +/− ischaemia, plus ↑ susceptibility to infection.

- Motor neuropathy → ↑ curvature and height of the arch of the foot → hyperextension and subluxation at metacarpophalangeal joints → clawing at the interphalangeal joints → pressure on metatarsal heads, heel, and clawed toes, the tips of toes, and over the proximal interphalangeal joints.
- Sensory neuropathy means patient does not perceive pain at the pressure points until too late (or not at all), so cannot avoid tissue injury. Patient may also sustain penetrating injuries or burns without realizing.
- Autonomic neuropathy → dry, fissured skin, which is more susceptible to injury and infection.
- Peripheral vascular disease, if present, ↓ healing of ulcers.
- ↓ leukocyte function ↑ risk of 2° infection.
- Progressive tissue destruction and/or deep infection may → need for amputation. Most patients undergoing amputation for non-traumatic causes are diabetic.

Diabetic foot infections are frequently polymicrobial. The extent of infection determines the likely pathogens (Table 14.2).

Clinical features

Wide clinical spectrum from superficial infections with local inflammation (erythema, swelling, pain, +/− purulent discharge); to deeper infections with systemic symptoms +/− osteomyelitis, draining sinuses or exposed bone; less commonly necrotizing fasciitis or septicaemia.

Diagnosis

Blood tests may show ↑ WBC, CRP, ESR, glucose, and creatinine. Plain foot X-rays may show gas in the soft tissues, bone destruction, and/or changes consistent with infection or diabetic osteopathy. Serial X-rays may show progressive changes over weeks. MRI is the best imaging modality in indeterminate cases.

Management

Assessment

- Assess for systemic features of sepsis (fever, cardiovascular stability, inflammatory markers), hydration, and diabetic control.
- Assess sensation, peripheral perfusion (peripheral pulses; Doppler assessment and ankle–brachial pressure indices if available).
- Look for cellulitis, necrosis, swelling, discharge, or crepitus.
- Debride ulcers to determine extent. If possible, probe with a sterile metal probe: palpable bone suggests underlying osteomyelitis. Other features suggestive of osteomyelitis include: ulcer size >2 × 2cm, ulcer depth >3mm, and ulcer duration >2wks.

Surgery

- Prompt surgery indicated (and may be limb-saving) if significant necrosis, abscess, crepitus, gangrene, or necrotizing fasciitis.
- Surgery (ideally with collection of deep samples for microbiology) also indicated for bone and joint involvement; timing depends on acuity and severity of presentation.
- Vascular surgery may be required if there is significant limb ischaemia and in some cases may avoid amputation.

Antibiotics

- See Table 14.2 for empiric antibiotic regimens.

Table 14.2 Antibiotic treatment of diabetic foot infections

Severity	Common microbiology	Treatment choices
Mild Superficial; <2cm erythema around ulcer, +/− purulent discharge	S. *aureus* (incl. MRSA)* BHS	1st: oral flucloxacillin 2nd: oral clindamycin 3rd: oral doxycycline 4th: oral co-trimoxazole
Moderate Local swelling or induration, >2cm erythema around ulcer, +/− purulent discharge	S. *aureus* (incl. MRSA)* BHS Gram negatives Anaerobes	1st: co-amoxiclav 2nd: ceftriaxone 3rd: ciprofloxacin + clindamycin
Severe Local infection signs plus SIRS/sepsis; or deep/limb-threatening infections.	As above, plus *Pseudomonas aeruginosa*	1st: piperacillin-tazobactam 2nd: co-amoxiclav + gentamicin 3rd: ciprofloxacin + clindamycin

*Methicillin resistant *Staph. Aureus* should be treated according to the isolate's antibiotic susceptibility or local policy.

Duration of antibiotic therapy

- Amputation through infected soft tissue, no residual infected bone: 1–2wks.
- Amputation/surgery through ischaemic or severely infected soft tissues, including deep tissue involvement (e.g. tendon sheaths): 4wks.
- Osteomyelitis, fully resected, with restoration of soft tissue cover: 4–6wks.
- Osteomyelitis with residual infected or dead bone: 6–12wks.

Prevention

- Prevent ulcers/promote ulcer healing by careful attention to foot care (daily foot inspection) and footwear off-loading pressure points.
- Optimize glycaemic control.
- Optimize BP control.
- Avoid smoking.

Fungal skin infections

Cutaneous infections

Dermatophytoses (tinea), see Colour Plate 22a, 22b.

Common skin infections caused by fungi, particularly *Trichophyton* and *Microsporum* spp. Clinical presentations include:

- Scaling or maceration between toes (tinea pedis, or 'athlete's foot').
- Itchy, scaly, red rash with definite edges in the groin (tinea cruris).
- Annular lesions with raised edges (often itchy) anywhere on the body (tinea corporis).
- Scaling and itching of the scalp with loss of hair (tinea capitis).

Treatment is with local application of Whitfield's ointment (benzoic acid compound) or clotrimazole for 2–4wks. For severe cases and nail involvement, use 4–6wks of oral griseofulvin 10mg/kg (alternatives: terbinafine or itraconazole).

Pityriasis versicolor

A superficial, hypopigmented, macular rash normally of the upper body. Treat topically with 2% selenium sulfide shampoo (apply, lather, and leave in contact for 10min before rinsing); or with oral fluconazole 400mg as a single dose.

Superficial candidiasis

In addition to vaginal and oral infection, *Candida albicans* can infect moist folds of skin ('intertrigo'), producing a red rash and skin damage, e.g. in the groin, under breasts, nappy area of baby. Treat with topical nystatin or clotrimazole and keep dry.

Subcutaneous infections

Mycetoma (Madura foot)

- Chronic infection of subcutaneous tissue, bone, and skin that is due to environmental fungi (eumycetes → eumycetomas) or bacteria (actinomycetes or *Nocardia* spp. → actinomycetomas).
- Usually follows inoculation by penetrating injury (e.g. thorn).
- Local induration and swelling may be followed by formation of multiple sinus tracts (Fig. 14.1), involvement of lymphatics, and spread from subcutaneous tissue to involve bone. Pain rarely severe.
- Macroscopic colonies of slow-growing bacteria or fungi appear like 'grains' that may be discharged from sinuses.
- Most commonly occurs on the foot, but may occur anywhere.

Diagnosis

- X-ray: may be expansion and erosion of underlying bone.
- Microscopy sinus discharge (+/− culture/biopsy) to identify cause.

Management

- Fungal mycetomas rarely respond to systemic antifungals alone and usually require wide local excision or amputation.
- Actinomycetomas may be treated with co-trimoxazole 960mg bd po for several months (until clinical resolution), plus streptomycin or dapsone for the first 1–3mths of treatment.

Sporotrichosis

- Follows inoculation of environmental dimorphic fungus *Sporothrix schenckii* into the skin at sites of minor trauma.
- May present as single ulcer or nodule, or spread along lymphatics forming nodules at intervals that may ulcerate.
- Chronic lesions may look like psoriasis or a granuloma.

Treatment Itraconazole for localized disease; amphotericin B for severe/disseminated infection.

Chromoblastomycosis

- Follows traumatic inoculation of a range of dark-walled (dematiaceous) fungi found in the soil, e.g. *Fonsecaea pedrosoi*.
- Scaly papules, nodules and plaques develop that may become lobulated, often with black dots comprising fungi and necrotic debris.
- Chronic lesions may look like psoriasis or a granuloma.

Treatment Itraconazole +/− topical cryotherapy; curettage may → spread.

Other fungal skin infections

- Systemic mycoses such as histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and other fungal infections in immunocompromised individuals, may also involve the skin.
- Clinical signs vary, but include purpura, ulcers, slow-spreading verrucous plaques, nodules, papules, pustules, and abscesses.
- Treatment depends on the aetiology and immune status of the host, but includes systemic antifungals and surgical debridement.

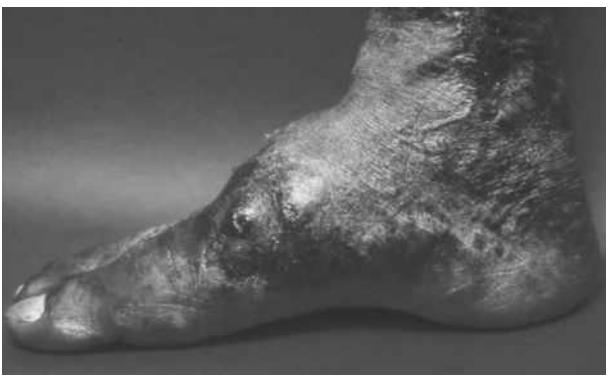

Fig. 14.1 Madura foot: fungal mycetoma caused by *Fusarium* spp.

Chapter 15

Sexually transmitted infections

Henrietta Williams

Why are sexually transmitted infections important?

STIs significantly impact the health of individuals and the population:

- *Acute problems*: urethral/vaginal discharge, pain, fever.
- *Chronic problems*: pelvic pain, infertility, tubal pregnancy, malignancy, miscarriages, perinatal infection, neurological and cardiovascular disease.

In addition:

- Stigma may ↓ psychological health and well-being.
- Prevalence is ↑ among the most vulnerable and marginalized groups in society that, combined with the stigma, → difficulties in accessing healthcare.
- Many STIs ↑ risk of HIV transmission.

Developments in effective preventative interventions for HIV, including male voluntary circumcision, treatment as prevention, pre-exposure prophylaxis (PrEP), and post-exposure prophylaxis (PEP) have had an impact on HIV and STI control in many communities. Recognizing the impact of these interventions is crucial in the planning of effective public health policy.

Epidemiology and control of STIs

The May and Anderson equation encapsulates important factors in the epidemiology of STIs. This states that:

$$R_0 = BCD$$

where: R0 is the number of 2° cases resulting from an infected individual in a susceptible community; B is the probability of an infection being transmitted per sexual activity; C is the rate of change of sexual partners; and D is the average duration of infectiousness.

Factors influencing these variables are listed in Table 15.1. Successful public health interventions to control STIs need to reach 'core groups' in which ↑ STI prevalence is usually associated with frequent changes of partner and unsafe sexual practices. Such groups include commercial sex workers, men who have sex with men (MSM), and sexually active adolescents.

Challenges and opportunities in control of STIs

Viral STIs (e.g. HSV and HPV) have additional challenges, compared to bacterial STIs (e.g. gonorrhoea, syphilis, and chancroid). Lack of curative treatment for viral STIs and poor accessibility to suppressive treatment → symptomatic or asymptomatic viral shedding and ongoing transmission. HSV-2 is often a commoner cause than chancroid of genital ulceration. There are, however, new preventative measures.

Vaccines

Recently developed HPV vaccines can ↓↓ HPV-related disease, including cervical cancer and genital warts (➲ Immunization, p. 853).

Male circumcision

↓ transmission of HIV from women to men by ~60%. In countries where heterosexual HIV transmission predominates, HIV prevalence is high, with low rates of male circumcision. If circumcision can be carried out safely, it can ↓ HIV transmission. There is also evidence that MSM who practice insertive anal sex also have some protection from acquiring HIV if they are circumcised. Information available at: http://www.who.int/hiv/topics/malecircumcision/en/index.html.

Table 15.1 Variables influencing the reproductive rate (R_0) of an STI. R_0 = BCD

Variable	Factors impacting these variables
Probability of an STI being transmitted (B)	• Condom usage • Sexual practices, e.g. 'dry sex', anal sex, condomless sex • Treatment of other STI • Circumcision • Suppressive treatment, e.g. HSV
Rate of change of sexual partners (C)	• Safer sexual behaviour patterns • ↓ partner change (especially concurrent partners) • Delayed initiation of sexual intercourse
Average duration of infectiousness (D)	• Education and awareness of STI • Availability and access to diagnostic and treatment services • Availability and access to syndromic treatment • Screening of high-risk individuals

Syndromic management of sexually transmitted infections

Rapid, definitive diagnosis and treatment of STIs, together with partner notification, ↓ transmission and reinfection. Rapid point-of-care diagnostic tests are increasingly available and should be used when possible. Where they are not available, STI services focus on syndromic management treatment algorithms to cure common causes of defined clinical syndromes. HCWs are trained to identify these syndromes by easily recognizable symptoms and signs.

Syndromic management is aimed only at symptomatic patients. Treatment reflects prevalence data and local antibiotic resistance patterns. To ↑ compliance, directly observed, single-dose treatment is used whenever possible. Syndromic management also includes partner notification and sexual health promotion.

Advantages of syndromic management

- Prompt and rapid treatment at the point of presentation.
- Does not need expensive or sophisticated laboratory.
- Does not need highly trained laboratory staff.
- Involves locally trained HCWs.

This section outlines the management of the following STI syndromes:

- Urethral discharge.
- Vaginal discharge.
- Lower abdominal pain in women.
- Scrotal swelling.
- Genital ulcer disease.
- Inguinal buboes.
- Neonatal conjunctivitis.

See: http://www.who.int/hiv/pub/sti/pub6/en/.

Urethral discharge in men

Urethritis is diagnosed if urethral discharge or an inflamed meatus is seen on examination (Colour plate 31), or dried discharge is seen on the penis.

Clinical features

Most common presentation is urethral discharge and dysuria. In men, the urethra can be 'milked' to detect the presence of a discharge.

Cause

- Most common pathogens: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*.
- Less common pathogens: genital mycoplasmas (*Mycoplasma genitalium*), *Trichomonas*, HSV, and *Adenovirus*.
- In ~50% of cases, no pathogen identified.
- Sexual behaviour may predict aetiology: e.g. HSV and *Adenovirus* are common in those practising insertive oral sex.

Diagnosis

If laboratory is available, a sample of discharge can be swabbed for culture and air-dried on a glass slide for microscopy. Gram –ve intracellular diplococci suggest *N. gonorrhoeae*. Presence of >5 pus cells in a Gram smear has been used to confirm the presence of urethritis, but this may not be sufficiently sensitive.

Management

- Treatment of the index case.
- Partner notification.
- Treatment of contacts.

If gonorrhoea cannot be reliably excluded, treatment should be for both gonorrhoea and *Chlamydia* (➲ Chlamydial infections, p. 618), ideally with single-dose treatment to ↑ adherence. The index patient should return if symptoms persist for >7d. Persistence suggests failure of treatment or reinfection. If reinfection unlikely, refer for laboratory investigations to identify less common causative pathogens; if no laboratory investigations are available, treat for trichomoniasis or *M. genitalium*.

Recommended treatment regimens Therapy for uncomplicated gonorrhoea (➲ Gonorrhoea, p. 617) plus therapy for uncomplicated *Chlamydia* (➲ Chlamydial infections, p. 618).

Alternative regimen if tetracyclines are contraindicated/not tolerated Therapy for uncomplicated gonorrhoea (➲ Gonorrhoea, p. 618) plus erythromycin 500mg oral qds for 7d.

Vaginal discharge

The usefulness of vaginal discharge as a symptom in syndromic management of STIs is uncertain. Personal and cultural factors influence the subjective interpretation of vaginal discharge so it does not reliably indicate cervical infection. Vaginal speculum examination when feasible can confirm the presence of discharge and view the cervix. Cervicitis in a woman with vaginal discharge makes an STI much more likely. Bacterial vaginosis remains a common cause of vaginal discharge (Colour Plate 32).

Clinical features

Abnormal vaginal discharge is usually caused by vaginitis or vaginosis; cervicitis (often an STI) is common and cannot be reliably distinguished from symptoms alone. Cervical mucus or pus, presence of cervical erosions, cervical friability, and intermenstrual or postcoital bleeding are more frequent in cervicitis, but do not exclude vaginitis or vaginosis. Risk assessment (➲ Management) takes account of local STI prevalence, as well as local sexual behaviour patterns.

Causes

Bacterial vaginosis, candidiasis, trichomoniasis; also cervical infection caused by *Chlamydia* spp. and *Neisseria gonorrhoeae* and, less commonly, *M. genitalium*. These cervical infections are frequently asymptomatic. Non-infective causes of vaginal discharge usually are less acute and include malignancy, foreign body, atopic vulvovaginitis, and cervical ectropion.

Diagnosis

History of the discharge and associated symptoms, as well as a risk assessment. If available, a Gram stain for *N. gonorrhoeae* from the cervix and a wet preparation for *Trichomonas* from the vagina are helpful. Nucleic acid amplification testing (NAAT) if available should include tests for *C. trachomatis*, *N. gonorrhoea*, and *M. genitalium*.

Management

Treat for vaginitis; also treat women for common causes of cervicitis if they have STI risk factors:

- <21yrs.
- Unmarried/not cohabiting.
- >1 sexual partner in <3mths.
- New partner in <3mths.
- Current partner with an STI.

Treatment

- *Cervicitis*: therapy for uncomplicated gonorrhoea (➲ Gonorrhoea, p. 617) and *Chlamydia* (➲ Chlamydial infections, p. 618).
- *Vaginitis*: therapy for bacterial vaginosis (➲ Bacterial vaginosis, p. 623; Colour Plate 32) and *Trichomonas vaginalis* (➲ Trichomoniasis, p. 622), and, if indicated, for *Candida albicans* (➲ Candida vaginitis, p. 626).

Lower abdominal pain in women

Endometritis, salpingitis, and pelvic inflammatory disease (PID) resulting from STI can present with lower abdominal pain in sexually active women. PID may also occur in the absence of STI; in these cases, the aetiology is often polymicrobial and may result from inadvertent introduction of flora from the lower genital tract, e.g. during a gynaecological procedure.

Causes

Causes of PID include *Chlamydia* and gonorrhoea and, less commonly, genital mycoplasmas. Non-STI pathogens responsible for PID include *Actinomyces*, TB, anaerobes, and *Mobiluncus*.

Diagnosis

In addition to lower abdominal pain, PID commonly presents with fever, vaginal discharge, deep dyspareunia, menstrual disturbance, and sometimes N&V. Signs include fever, lower abdominal tenderness, vaginal discharge, uterine tenderness, pain with movement of the cervix (cervical excitation), and adnexal tenderness and/or adnexal masses. Clinical examination has low diagnostic sensitivity and specificity for PID and no reliable non-invasive investigations exist. Have a low threshold for treatment: delay ↑ risk of long-term sequelae.

Management

Admit to hospital if severely unwell, for surgical emergencies (e.g. ectopic pregnancy, appendicitis), during pregnancy, if a pelvic abscess suspected, or if outpatient treatment has failed. PID is often polymicrobial, so treatment should be broad spectrum, while targeting common bacterial causes.

Treatment

Local epidemiology and antibiotic resistance patterns should always be considered.

Outpatient treatment

Treat for gonorrhoea (➲ Gonorrhoea, p. 617), plus doxycycline 100mg bd (or tetracycline 500mg qds) plus metronidazole 400mg bd for 14d. Avoid alcohol with metronidazole and avoid tetracyclines in pregnancy.

Inpatient treatment

- Ceftriaxone 2g IV daily for 7d, plus doxycycline 100mg oral/IV bd (or tetracycline 500mg oral qds) and metronidazole 400–500mg bd oral/IV (or chloramphenicol 500mg oral/IV qds) for 14d *or*
- Clindamycin 900mg IV tds plus gentamicin 1.5mg/kg tds or substitute single-dose regimen.
- Ciprofloxacin 500mg oral bd plus doxycycline 100mg oral/IV bd (or tetracycline 500mg oral qds) and metronidazole 400–500mg oral/IV bd (or chloramphenicol 500mg oral/IV qds).

For inpatient regimens, continue IV treatment for 2d after severe symptoms improving and then treat for a further 14d with doxycycline 100mg oral bd or tetracycline 500mg oral qds.

If an intrauterine contraceptive device (IUD) is present and PID is mild, it is reasonable to leave IUD *in situ*, if the patient is monitored for improvement. If an IUD is to be removed, usually recommended >48h of antibiotics. Alternative contraception will be needed.

Scrotal swelling

Testicular torsion

Should always be excluded in patients with a painful swollen scrotum. In acute torsion there is usually severe pain, worse when walking, which is not relieved by supporting the testicle. Often associated N&V. Testicle may be red and swollen. Urgent surgical exploration is needed as the testicle will not survive for >6h with compromised blood supply.

Epididymitis

This is one of the commonest causes of scrotal swelling. In young, sexually active men this is usually due to an STI and often associated with orchitis. Infective causes of epididymitis or epididymo-orchitis may be either STIs or non-STIs. In men >35yrs (and in children and adolescents prior to sexual debut), non-STIs are more common. Associated urethral discharge strongly indicates an STI.

- *STIs*: *Chlamydia* and gonorrhoea.
- *Non-STIs*: *Escherichia coli*, *Klebsiella* spp., or *Pseudomonas aeruginosa*. TB and *Brucella* infection may also need to be considered. Rarer causes include *M. leprae* reactions, syphilis, *Candida albicans, Streptococcus pneumoniae*, and *Haemophilus influenzae* type b. Mumps can → orchitis.

Non-infectious causes of scrotal swelling include malignancy and trauma.

Management

Treatment for *Chlamydia* and gonorrhoea if suspected; bed rest, support of the testicle, NSAIDs for pain.

Recommended treatment regimens

- *If likely STI*: treat as for uncomplicated gonorrhoea (➲ Gonorrhoea, p. 617) plus treatment of *Chlamydia* with 14d doxycycline 100mg bd (➲ Chlamydial infections, p. 618).
- *If not likely to be STI*: treat coliforms with ciprofloxacin 500mg bd for 10d. If severe, cefuroxime 1.5g tds IV + gentamicin for 3–5d.

Genital ulcer

Causes

Genital ulcer disease often has multiple aetiologies. Ulceration caused by syphilis, lymphogranuloma venereum (LGV), granuloma inguinale, chancroid, and HSV cannot be reliably distinguished clinically. HSV-2 is common, even in areas where other causes of genital ulceration are common. Unusual or atypical presentations are common in HIV+ve patients. 2° bacterial infection of genital ulcers is common.

Diagnosis

Offer serological testing for syphilis and HIV. Swab ulcer and test for HSV (if available) and *Treponema pallidum*, either by dark ground microscopy or other method if available (e.g. NAAT). Consider chancroid and donovanosis, depending on local prevalence. Microscopy with Giemsa staining may help diagnose donovanosis and culture can diagnose chancroid. In some places, a multiplex PCR is available for genital ulcer diagnosis (syphilis, HSV, chancroid, and donovanosis).

Management

Counsel on infectivity of HIV and syphilis, and natural history of HSV and its transmission. Treatment should cover syphilis and HSV. Treatment for LGV, granuloma inguinale, and chancroid depends on local prevalence rates. Advise patient to return if not healed <7d. Individuals with HSV/HIV co-infection often have persistent multiple lesions and are at ↑ risk of transmitting HIV. HIV–ve patients with genital HSV are more susceptible to contracting HIV infection.

Recommended treatment

- Therapy for syphilis (➲ Syphilis, p. 613) *plus*
- Therapy for HSV if available (➲ Genital herpes, p. 565) *plus*
- Therapy for chancroid (➲ Chancroid, p. 620) *or*
- Therapy for granuloma inguinale (➲ Granuloma inguinale (donovanosis), p. 621) *or*
- Therapy for LGV (➲ Lymphogranuloma venereum, p. 619).

Inguinal buboes

These are localized enlarged lymph nodes in the groin; tender +/− fluctuant. LGV and chancroid are common causes. They are usually other signs of an STI; chancroid is usually associated with a genital ulcer.

Recommended treatment

Ciprofloxacin 500mg oral bd for 3d plus *either* doxycycline 100mg oral bd *or* erythromycin 500mg oral qds for 14d or longer as needed. Fluctuant lymph nodes can be aspirated through skin, but should not be incised or drained as this can ↓ healing. Biopsy for diagnosis if treatment fails.

Neonatal conjunctivitis

Can be caused by *N. gonorrhoeae*, *Chlamydia*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus* spp. *N. gonorrhoeae* is an important common cause—without appropriate treatment it can → blindness.

Diagnosis

A red swollen sticky eye occurs 2–5d after delivery in gonococcal conjunctivitis and at 5–12d in chlamydial conjunctivitis.

Management

- Treat both gonorrhoea and *Chlamydia*.
- *Treatment of gonococcal neonatal conjunctivitis*: ceftriaxone 50mg/kg (max. 125mg) IM stat.
- *Treatment of chlamydial neonatal conjunctivitis*: erythromycin syrup 50mg/kg oral daily in four divided doses for 14d *or* trimethoprim 40mg with sulfamethoxazole 200mg oral bd for 14d.

Prevention

Neonatal gonococcal conjunctivitis can be prevented by washing carefully at the time of birth and applying 1% silver nitrate solution or 1% tetracycline ointment to eyes. Recommended for all babies born to mothers at high risk of gonorrhoea. Provides little protection from *Chlamydia*, which may also be present.

Syphilis

A worldwide disease caused by the spirochaete *Treponema pallidum*. In developed countries, there has been ↑ incidence of infectious syphilis in MSM. Syphilis can be divided into four stages:

- Local 1° infection.
- Dissemination associated with 2° syphilis.
- A latent period during which infectivity is low (relapses into 2° syphilis may occur during the 1st 4yrs after contact—early latent period).
- Late syphilis (>2yrs' duration) occurs after many years with widespread gumma formation (granulomatous lesions with a necrotic centre and surrounding obliterative endarteritis) and long-term damage to the cardiovascular and CNS.
- Neurological involvement may occur at any stage of syphilis, not just as a late complication. Among MSM, early syphilis often presents with neurological symptoms.

Transmission

Commonly through abraded skin at sites of sexual contact. Other modes include congenital transmission (→ severe disease in the infant; Box 15.1) and blood transfusion.

Clinical features

Primary syphilis

9–90d after infection a 1° genital ulcer or chancre forms. Typically solitary, 'punched out', indurated, and painless, with a clear exudate. Atypical lesions occur, e.g. multiple ulcers in HIV+ve individuals. Chancres are highly infectious and resolve over a few weeks. There is painless regional lymphadenopathy.

Secondary syphilis

Coincides with the greatest number of treponemes in the body and blood, 1–6mths after contact.

- A transient, variable (but not vesicular) rash, particularly on trunk, soles, and palms. Not itchy.
- In warm, moist areas where two skin surfaces are in contact (e.g. perineum), papules enlarge and coalesce to form highly infectious plaques called condylomata lata.
- Silver-grey lesions with red periphery on mucosal surfaces called mucous patches (e.g. snail track ulcers in the mouth).

There is also:

- Low-grade fever.
- Malaise.
- Generalized lymphadenopathy.
- Arthralgia.
- Occasionally, focal involvement of eyes, meninges, parotid glands, or viscera (kidney, liver, GI tract).
- 2° syphilis symptoms generally resolve spontaneously <12mths.

Late syphilis

Areas of local gummatous tissue destruction in skin, bones, liver, and spleen are common. Other manifestations:

- Ascending aortic aneurysm +/– aortic regurgitation.
- Coronary artery stenosis.
- Chronic meningitis → cranial nerve damage, hemiparesis, seizures.
- CNS parenchymal disease (general paralysis of the insane)—psychoses, dementia, hyperactive reflexes, tremor, speech, and pupillary disturbances (Argyll–Robertson pupils).
- Tabes dorsalis: shooting pains in limbs, peripheral neuropathy, ataxia, Charcot's joints, +ve Romberg's sign.

Diagnosis of syphilis

- *Dark-field microscopy*: of ulcer exudate for motile spirochaetes.
- *PCR and fluorescence staining of exudates*: increasingly available, useful for oral/GI specimens because of potential confusion with commensal spirochaetes on dark-field microscopy.
- *Serology*: either specific (fluorescent *Treponema* antibody, *Treponema pallidum* haemagglutination assay) for exposure, or non-specific (VDRL, rapid plasma reagin (RPR)) for active disease and screening. An enzyme immunoassay (EIA) detects anti-treponemal IgG and IgM: IgM usually detectable towards the end of 2nd week, and IgG in 4–5th week of 1° infection.
- *CSF examination*: should be performed in any patient with neurological symptoms or signs. It remains controversial whether asymptomatic patients need CSF examination. Recommendations include early syphilis with neurological symptoms or signs, late latent (>2yrs) syphilis with an RPR >32, HIV+ve individuals with latent syphilis, and patients with inadequate serological response to treatment. CNS can be involved in any stage of syphilis.
- *HIV testing*: should be offered to all patients with syphilis since dual infection is common, and affects assessment and management.

Management

Early syphilis (stages 1 and 2 or latent syphilis of <2yrs' duration)

- Either benzathine benzylpenicillin 2.4 million units IM stat (usually given as two injections into separate sites because of the large volume).
- *Or* procaine benzylpenicillin 600,000 units IM od for 10d.

For penicillin-allergic patients, alternatives include:

- Either tetracycline 500mg oral qds for 14d.
- Or doxycycline 100mg oral bd for 14d.
- Or erythromycin 500mg oral qds for 14d for penicillin allergic *pregnant* patients.

Follow up at 3, 6, and 12mths to assess treatment and possible reinfection.

Late syphilis (not neurosyphilis; includes latent syphilis of >2yrs or indeterminate duration)

- Either benzathine benzylpenicillin 2.4 million units IM (given as two injections into separate sites) once-weekly for 3wks.
- Or procaine benzylpenicillin 600,000U IM od for 17d.

For penicillin-allergic patients, alternatives include the following (however, penicillin is preferred therapy and should be given whenever possible):

- Either tetracycline 500mg oral qds (probably better) for 30d.
- Or doxycycline 100mg oral bd, for 30d.
- Or erythromycin 500mg oral qds for 30d.

Neurosyphilis

- Either aqueous benzylpenicillin 2–4 million units IV every 4h for 14d.
- Or procaine benzylpenicillin 1.8–2.4 million units IM od plus probenecid 500mg oral qds for 17d: ensure patient compliance with this outpatient regimen.

For penicillin-allergic patients, alternatives include:

- Tetracycline 500mg oral qds for 30d.
- Doxycycline 200mg oral bd for 28d.

Consult a neurologist if possible and follow up carefully.

Management of syphilis in pregnancy

Pregnant women with syphilis should be treated with penicillin whenever possible. Pregnant women who are allergic to penicillin, but without anaphylaxis, may be given ceftriaxone 1g od for 10d. Desensitization to penicillin should be considered in a hospital setting. Alternatives include erythromycin 500mg oral qds for 14d (early syphilis) or 30d (other forms of syphilis). *Note*: effectiveness of erythromycin is uncertain, esp. for neurosyphilis, and many failures have been reported. Tetracyclines are contraindicated in pregnancy. The baby should be evaluated and treated soon after birth.

Box 15.1 Congenital syphilis

Syphilis causes ~200,000 stillbirths annually, most of which are preventable through screening and treatment in pregnancy, as previously described. Transplacental infection may occur during any stage of syphilis, but is most likely during the early stages. If untreated → premature delivery or perinatal death in ~40–50%. Untreated late maternal infection ↑ perinatal mortality and 10% of children will be born with congenital syphilis.

Features of congenital syphilis include rhinitis, a diffuse maculopapular, desquamative rash involving palms and soles (may be vesicular/bullous), hepatosplenomegaly, lymphadenopathy, generalized osteochondritis/periostitis, CNS involvement, anaemia, jaundice, and thrombocytopenia, although any organ may be affected and some newborns are asymptomatic. Death may occur, e.g. due to pneumonia, liver failure, pulmonary haemorrhage, or hypopituitarism.

In those children who survive the neonatal period, infection normally becomes latent, but there may be sequelae involving the bones (frontal bossing, saddle nose, protruding mandible, short maxilla, saber tibia), joints (recurrent arthropathy and effusions), teeth (peg-shaped upper incisors—'Hutchinson's teeth'), eyes (interstitial keratitis), and neurological system (neurosyphilis, deafness).

Diagnosis

Often clinical, supported by routine bloods, X-rays (look for raised periosteum on plain X-rays of the long bones), VDRL/RPR on blood and CSF, +/– specific serology and/or PCR if available. Test the mother. Treatment is cheap and safe, so all children born to infected mothers should be treated, even if mother received treatment during pregnancy.

Management

Early congenital syphilis (<2yrs) and infants with abnormal CSF

- Either aqueous benzylpenicillin 100,000–150,000U/kg/d administered as 50,000U/kg IV bd for the first 7d of life and then tds for a total of 10d.
- Or procaine benzylpenicillin, 50,000U/kg IM od for 10d.

Congenital syphilis of 2yrs

- Aqueous benzylpenicillin, 200,000–300,000IU/kg/d, administered as 50,000IU/kg IV/IM every 4–6h for 10–14d.

Penicillin allergic patients

Penicillin is the treatment of choice in infants with congenital syphilis and alternatives should only be considered if there is a significant allergy to this antibiotic. An alternative (after the first month of life) is:

- Erythromycin 7.5–12.5mg/kg oral qds for 30d.

Gonorrhoea

Gonorrhoea results from infection with the Gram –ve diplococcus *Neisseria gonorrhoeae*. 1° infection usually involves the mucosa of the urethra, cervix, rectum, or oropharynx (➲ Colour plate 31).

Without early effective treatment, both local and disseminated complications occur. Strains are ↑ resistant to penicillin, tetracycline, doxycycline, azithromycin, and other antibiotics, and highly resistant gonorrhoea has been reported. Surveillance and control measures are important as resistance patterns change. Gonococcal ophthalmia neonatorum may → blindness if not treated early.

Clinical features

In *men*, urethral discharge and dysuria occur 2–5d after infection. Discharge is initially mucoid, becoming profuse and purulent (in contrast to non-gonococcal urethritis). Local complications include acute epididymitis, prostatitis, peri-urethral abscess, and urethral stricture.

In *women*, infection produces cervicitis (+/– urethritis) after ~10d with vaginal discharge, dysuria, intermenstrual bleeding, or postcoital bleeding. Unlike men, women are often asymptomatic. Local complications include PID and peri-hepatitis. Urinary frequency and urgency are uncommon symptoms in men and women.

Haematogenous dissemination can occur in untreated patients, → meningitis, endocarditis, osteomyelitis, sepsis, or acute destructive monoarthritis. Reactive polyarthropathy and papular/pustular dermatitis are recognized complications.

Diagnosis

Gram –ve intracellular diplococci in smears from the urethra in men (>90%) and endocervix in women (less reliable); culture. PCR testing may be available, which is more sensitive but in low-prevalence populations the +ve predictive value of a test may be low. To confirm a positive PCR, many centres also culture specimens to identify antibiotic susceptibility.

Management

Resistance to penicillin, tetracyclines, and fluoroquinolones is ↑. ↓ sensitivity to ceftriaxone (widely used therapy) is reported, so many guidelines now recommend dual antibiotic therapy. Consider local patterns of resistance when treating gonorrhoea and perform a test of cure 1wk after treatment (especially important for asymptomatic infections). See Box 15.2 for recommended regimens. Unless able to exclude *Chlamydia*, also treat for *Chlamydia*, since patients often co-infected. Treat sexual partners at the same time.

Box 15.2 Recommended regimens for gonorrhoea

In uncomplicated genital and anal infection
Ceftriaxone 500mg IM stat plus 1g azithromycin oral stat.

Other regimens depend on local resistance patterns. Always use the locally recommended regimen
Options include:
- Azithromycin 2g oral single dose *or*
- Spectinomycin 2g IM single dose.
- Ciprofloxacin 500mg oral stat (not during pregnancy). Widespread resistance so only use if susceptibilities known before treatment.

In disseminated infection
- Ceftriaxone 1g IV/IM od for 7d *or*
- Spectinomycin 2g IM bd for 7d.
- Switch to oral route after 48h if response is good, e.g. cefixime 400mg bd oral, or ciprofloxacin 500mg bd oral.
- Extend treatment to 14d in meningitis, and 28d in endocarditis.

Gonococcal conjunctivitis in adults is highly contagious. Manage with barrier nursing, frequent saline irrigation, and antibiotics: ceftriaxone 1g IM single dose (or ceftriaxone 500mg od IM for 3d) plus 1g azithromycin oral stat.

If penicillin allergy:
- Azithromycin 2g oral stat, plus doxycycline 100mg bd oral for 1wk, plus ciprofloxacin 250mg od oral for 3d.
- Spectinomycin 2g IM od for 3d.

Neonatal gonococcal conjunctivitis See ➔ Conjunctivitis p. 617, Neonatal conjunctivitis, p. 611.
- Ceftriaxone 50mg/kg (max. 125mg) IM stat.
- Neonatal patients should be reviewed at 48h.

Chlamydial infections

Chlamydia trachomatis is an obligate intracellular bacterium. *Chlamydia* serovars D–K are the most common STI in resource-rich regions. Frequently coexists with gonorrhoea, and is the commonest cause of non-gonococcal urethritis in men. These serovars cause infection of the urethra, endocervix, or rectum, and may → PID in women and epididymo-orchitis in men; less commonly → conjunctivitis, arthritis, and peri-hepatitis.

Other serovars include:

- Serovars L1–L3, which → lymphogranuloma venereum.
- Serovars A–C are not sexually transmitted, but cause trachoma (➲ Trachoma, p. 530).

Uncomplicated urethritis/endocervicitis/proctitis

Clinical features Infections in women are often subclinical or asymptomatic.

Diagnosis

Screening asymptomatic women at risk of infection → ↓ complications. Tests to detect *Chlamydia* DNA in urine (= do not require cervical or urethral swabs) are widely available and reliable for diagnosis of asymptomatic individuals. These tests have now replaced culture and other tests in many areas, especially for screening purposes.

Management

First choice is single-dose azithromycin 1g (directly observed where possible) for uncomplicated genitourinary infection. This eliminates need for a test of cure as adherence is not an issue; cure rates are 90%, and resistance is not documented.

Complicated chlamydial infections

Clinical features

Complications in men incl. epididymitis and epididymo-orchitis and (in MSM) chronic proctitis. Infections in women may → cervicitis, salpingitis, and endometritis. *Chlamydia* is a major cause of female infertility.

Management Doxycycline 100mg oral bd for 2wks +/– azithromycin 1g oral stat (➲ Syndromic management of sexually transmitted infections, p. 606).

Lymphogranuloma venereum

LGV is a chronic STI caused by the L1, L2, and L3 serovars. LGV is endemic in many parts of the world and affects MSM (often co-infected with HIV) in resource-rich countries.

Clinical features

1° lesion is a painless genital ulcer (rarely visible in women) that heals in a few days. After a latent period (days to months), acute, fluctuant inguinal lymphadenopathy (buboes) develop. Buboes may spread locally and ulcerate → sinuses/fistulae. Chronic blockage of lymphatic drainage → genital lymphoedema, often severe in women.

Diagnosis

This is by ELISA, DNA probe, direct fluorescent antibody test, or culture of bubo aspirate. Serology helpful if a fourfold rise in titre or a single titre of >1:64; a –ve antibody test rules out the diagnosis. Specific serovars responsible for LGV can be identified in some laboratories.

Management

Doxycycline, erythromycin, or tetracycline for 2wks, see Box 15.3. In LGV, fluctuant lymph nodes should be aspirated through healthy skin. Incision and drainage or excision of nodes will delay healing and is contraindicated (late sequelae such as stricture/fistula may require surgery). Partner notification and treatment is important. In many centres, MSM with rectal chlamydial infection are tested for LGV serovars, recognizing that LGV is not easy to diagnose clinically.

Box 15.3 Antibiotic regimens for chlamydial infection

Uncomplicated anogenital infection

- Doxycycline 100mg oral bd for 7d *or*
- Azithromycin 1g oral stat.
- *Alternatives*: amoxicillin 500mg oral tds for 7d, *or* erythromycin 500mg oral qds for 7d, *or* ofloxacin 300mg oral bd for 7d, *or* tetracycline 500mg oral qds for 7d.

Uncomplicated anogenital infection during pregnancy Erythromycin (base/ethylsuccinate) 500mg oral qds for 7d *or* amoxicillin 500mg oral tds for 7d.

LGV

- Doxycycline 100mg oral bd for 14d *or*
- Erythromycin 500mg oral qds for 14d.
- *Alternative*: tetracycline 500mg oral qds for 14d.

Neonatal chlamydial conjunctivitis

- Erythromycin syrup 50mg/kg/d in four divided doses for 14d.
- *Alternative*: co-trimoxazole 240mg oral bd for 14d.

Chancroid

An acute STI caused by *Haemophilus ducreyi* characterized by painful necrotizing ulceration and painful bubo formation; highly infectious and a common cause of genital ulcers in Africa and SE Asia. Chancroid is commoner in males, females may be carriers.

Clinical features

- 3–7d post infection, painful papules form, which rapidly → soft ulcers with undermined, ragged edges.
- Ulcers are haemorrhagic and sticky (often 2° infected); if multiple they may become confluent; they occur at sites of trauma during intercourse—extragenital ulcers are rare.
- 7–14d later inguinal nodes may become involved: painful, matted, and tethered to erythematous skin → bubo. A discharging sinus may develop, in time becoming a spreading ulcer. Lesions heal slowly and commonly relapse.

Diagnosis

- Clean ulcer with saline, then remove material from the undermined edge; or aspirate pus from bubo.
- *Gram stain smear*: *H. ducreyi* are Gram –ve rods (fine, short, round-ended) sometimes seen in 'shoal-of-fish' or 'railroad track' formation.
- *Culture is difficult*: PCR, immunofluorescence, and serology may be available in some laboratories.
- *Without treatment*: infectivity may continue for several months, but with appropriate antibiotic therapy (➲ Box 15.3, p. 619) lesions heal in 1–2wks. As with all STIs, intercourse should be avoided until lesions have completely healed.

Management

- Erythromycin 500mg oral qds for 7d.
- *Alternatives*: ciprofloxacin 500mg oral bd for 3d, *or* azithromycin 1g oral stat, *or* ceftriaxone 250mg IM stat.

Single-dose treatments have higher failure rates than longer courses of antibiotics, so erythromycin is treatment of choice. With HIV co-infection treatment is less effective. Co-infection of syphilis and HSV may occur.

Granuloma inguinale (donovanosis)

Klebsiella granulomatis (formerly known as *Calymmatobacterium granulomatis*) causes chronic, destructive ulceration of genitals and surrounding tissues. Males are more frequently infected. It is not easily transmitted; patients' sexual partners are often uninfected.

Clinical features

- 1–6wks following infection a painless indurated papule forms, which slowly develops into a 'beefy' granulomatous ulcer with characteristic rolled edges. Lesion is elevated, well defined, and bleeds easily.
- Usual sites are anogenital, thighs, and perineum; rarely vaginal (or rectal) lesions may present with PV (or rectal) bleeding. Healing is uncommon without treatment; 2° infection can follow → painful, destructive lesions, and may → SCC.
- Inguinal nodes are not involved unless there is 2° infection.
- Subcutaneous granulomas form, which may be mistaken for enlarged lymph nodes ('pseudo-bubo'). These may → abscess, discharging via a sinus, or an infected ulcer.
- Lymphoedematous enlargement of genitalia may occur during healing.

Diagnosis

- Crush a piece of granulation tissue from the active edge of the lesion between two slides, air dry, and stain with Giemsa or Gram stains.
- Look for large mononuclear cells filled with Donovan bodies (intracytoplasmic Gram –ve rods that look like closed safety pins due to bipolar staining).
- Culture is difficult; PCR and serology are available in some facilities.

Management

Treatment should be for at >3wks or until all the lesions have epithelialized.

- Azithromycin 1g oral stat then 500mg od.
- Doxycycline 100mg oral bd.
- *Alternatives*: erythromycin 500mg oral qds, *or* tetracycline 500mg oral qds, *or* co-trimoxazole 960mg oral bd.

Trichomoniasis

Clinical features

~50% of women with *Trichomonas vaginalis* infection are asymptomatic. Infection in men is usually asymptomatic, but may → urethritis. Vaginitis due to *T. vaginalis* can → irritating, pruritic (rarely foul smelling) discharge 5–28d post infection, +/– dyspareunia. Urethral infection may cause dysuria. The vaginal discharge is often copious, sometimes yellow or green, and pools in the posterior fornix. The vagina and cervix become inflamed; colposcopy reveals cervical haemorrhages in ~50% of symptomatic cases—'strawberry cervix' (this can also be seen by the naked eye during speculum examination in ~5% of women with trichomoniasis).

Diagnosis

Diagnose women by wet preparation microscopy of vaginal discharge for motile *T. vaginalis* (sensitivity 40–80%). Culture of vaginal discharge has a sensitivity of ~80%. Cervical smears often identify *Trichomonas*, but there is a significant risk of both false –ves and false +ves.

Diagnosis in men is difficult. *Trichomonas* can produce urethritis in men, but urethral swabs, urethral smears, and first-catch urine specimen are not sensitive in making a diagnosis. Often *Trichomonas* infection in men is only suspected and treated once other causes of urethritis have been excluded.

In some settings, sensitive PCR for *Trichomonas* is available.

Management of trichomoniasis

- Metronidazole 400–500mg oral bd for 7d.
- *Alternatives*: efficacy less certain; metronidazole 2g oral stat or tinidazole 2g oral stat.
- Sexual partners should be notified and treated.
- Patients should return after 7d if symptoms persist. Failure can be due to resistance or reinfection. Patients often respond well to retreatment with the 7d regimen.
- Refractory infections should be treated with metronidazole 2g oral od plus 500mg applied intravaginally each night for 3–7d.

Pregnancy

Treat with metronidazole in all trimesters of pregnancy, but avoid higher stat doses. Trichomoniasis in pregnancy can be treated with 5–7d of metronidazole 400–500mg oral bd. Trichomonas can be harmful in pregnancy, but there are no recommendations to screen for *Trichomonas* in asymptomatic pregnant women, as case detection and treatment has not been shown to improve outcomes.

Bacterial vaginosis

Bacterial vaginosis (BV) is a common cause of vaginal discharge (➔ Colour plate 32).

Characterized by:

- ↓ in hydrogen peroxide-producing lactobacilli.
- ↑ in other bacteria in greater amounts than normal in the vagina and include *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides*, *Mobiluncus*, peptostreptococci, and a recently identified bacterium *Atopobium vaginae*.

Clinical features

Commonly, an offensive, whitish discharge that tends to recur and may seem worse after intercourse. There is usually no itch or irritation. BV in non-pregnant women is associated with postpartum endometritis and surgical procedures (e.g. hysterectomy, termination of pregnancy). In pregnancy, it can → chorioamnionitis and amniotic fluid infection, ↑ rates of miscarriage (all trimesters), premature rupture of membranes, low birth weight, and preterm birth. BV ↑ susceptibility to and transmissibility of HIV.

Diagnosis

This is by microscopy; culture plays no part. Three of four of the following should be present for diagnosis:

- White, homogeneous vaginal discharge.
- Vaginal pH >4.5.
- Clue cells (>20% vaginal epithelial cells stippled with bacteria).
- A fishy smell on addition of KOH to a sample of vaginal discharge.

Management

- Metronidazole 400mg oral bd for 7d. A single dose of metronidazole 2g is an alternative if adherence poor.
- Clindamycin cream 2% intravaginally bd for 7d can be used as an alternative.
- Partners are not routinely treated as it is a polymicrobial condition and not an STI.

Women often have recurrences; >50% of women will have a recurrence <1yr. The trigger for ↓ in hydrogen peroxide-producing lactobacilli in the vagina is not understood. Optimal management of recurrent BV is unclear: 14d of metronidazole plus intravaginal clindamycin 2%, followed by monthly 2g doses of metronidazole may help. Pregnant women who are symptomatic should be treated. It is unclear whether treating asymptomatic pregnant women improves pregnancy outcomes. Although not classified as an STI, BV is not seen in women who have not had any sexual contact.

Genital herpes

Most genital herpes (➲ Colour plate 34) is caused by HSV-2, although there are ↑ number of 1° HSV-1 genital herpes infections.

- Recurrent genital ulcers are due to reactivation of latent virus from the dorsal root ganglia, occurring more frequently with HSV-2 than HSV-1.
- Asymptomatic shedding is common and is an important cause of transmission: most infections are transmitted by people unaware they are infected.
- HSV ↑ transmission of HIV and ↑ susceptibility to HIV.
- Persistence of HSV ulceration and frequent recurrences are common in HIV+ve individuals, and acute episodes are often prolonged, atypical and severe.

Transmission

Occurs by direct contact with infected genital secretions. After an incubation period of 2–7d, local infection and inflammation → multiple vesicular lesions that rapidly ulcerate.

Clinical features

See Colour Plate 34. The ulcers are greyish and extremely painful; they occur on the penis in men and the vagina, cervix, vulva, and perineum in women, often accompanied by a vaginal discharge. The ulcers may be present in the anus (usually in MSM). 1° infection is accompanied by fever, malaise, and inguinal lymphadenopathy; vulval oedema and urinary retention may occur. Extragenital involvement occurs in up to 20% of cases. Meningitis/encephalitis is a recognized complication. Non-1° initial infection (e.g. HSV-2 infection with pre-existing antibodies to HSV-1) is often less severe.

Diagnosis of genital herpes

Swabs from the lesion can be tested by PCR (highly sensitive), culture, or direct immunofluorescence. Reliable specific serological tests are available and so serological testing may be useful (e.g. for discordant couples) as part of preconception counselling.

Management

- Analgesia and salt baths may help ↓ discomfort and pain associated with 1° infections.
- *In those with a first clinical episode (take a careful history)*: aciclovir 200mg oral 5× daily for 5d, or valaciclovir 1g oral bd for 5d ↓ formation of new lesions, duration of pain, time required for healing, and viral shedding, but probably not the rate of future recurrence. Treatment should be started as soon as possible.
- *Recurrences*: can be managed with either episodic treatment or suppressive treatment. Episodic treatment is aciclovir 200mg oral 5× daily for 5d (*alternatives*: valaciclovir 500mg bd or famciclovir 125mg bd, for 5d). Patient-initiated high dose, short-course antivirals are also effective and safe: aciclovir 800mg tds for 2d, famciclovir 1g bd for 1d, or valaciclovir 500mg bd for 3d. Treatment should be started as soon

as early symptoms of recurrence are recognized; hence, these regimens are given in advance to patients to treat themselves.

- *Suppressive treatment*: usually considered if >6 episodes/yr. Regimens include aciclovir 400mg bd, famciclovir 250mg bd, or valaciclovir 500mg od. These regimens should ↓ recurrences by ~80%. If patients suffer from >10 episodes/yr, valaciclovir 1g od is often used. Recurrences become less common with ↑ duration, so try stopping antivirals after 1yr so that recurrence rates can be reassessed. Minimum continuous dose that will suppress recurrence should be determined empirically.
- *Decreasing transmission*: Condoms can ↓ transmission; long-term suppressive treatment with valaciclovir also appears to ↓ transmission. Lubrication with water-based lubricants is also advisable as trauma to the genitals can → recurrence.

Candida vaginitis

Candida vaginitis is not an STI. Occurs due to overgrowth of the commensal vaginal yeast, *Candida albicans* (and less commonly other *Candida* spp.). Antibiotic therapy, pregnancy, and immunosuppression all predispose to symptomatic candidiasis.

Clinical features

Commonly there is vulvitis, as well as vaginitis and intense vulval pruritus and erythema are characteristic. Discharge is thick, curd-like, and white (rarely it may only be scanty), and microscopy shows Gram +ve budding yeasts +/– hyphae; visualization of the yeasts is made easier by the addition of 10% KOH to clear the epithelial cells.

Recurrent vulvo-vaginal candidiasis is defined as >4 episodes of microbiologically proven *Candida* infection in a 12mth period; affects 5–8% of women in their reproductive life. The majority of women have no demonstrable risk factors and it may be due to a cell-mediated immunodeficiency at the vaginal mucosal level.

Men can suffer from *Candida* balanoposthitis, but this is not as a result of transmission between partners, and treatment of partners is not generally helpful unless the male partner is symptomatic.

Management

- Miconazole or clotrimazole 200mg intravaginally od for 3d *or*
- Clotrimazole 500mg intravaginally stat *or*
- Fluconazole 150mg oral stat.
- *Alternative*: nystatin 100,000IU intravaginally od for 14d, will treat all species of *Candida*.
- Women with recurrent vulvo-vaginal candidiasis can be treated with a 2wk induction course of clotrimazole followed by weekly maintenance treatment with clotrimazole 500mg as a pessary for 3–6mths. Alternatively, fluconazole 150mg oral can be given every 72h for three doses, then maintenance dose of 150mg oral once every week for up to 6mths.

Occasionally *Candida* vaginitis may be caused by a strain of *C. albicans* resistant to routine treatment, or to less common *Candida* spp., such as *C. glabrata* or *C. krusei*. Standard treatments should initially be used as *C. glabrata* may, e.g. be present as a commensal and not responsible for symptoms. Symptoms may be due to other *Candida* spp. or even genital pain syndromes. Nystatin 100,000IU intravaginally od for 14d is effective against all species of *Candida*. Extended and higher dose first-line treatments should also be considered for persistent symptoms, as well as boric acid pessaries, used intravaginally for 14d (if available). These are highly toxic, especially if taken orally, but can also be absorbed from skin and mucous membranes causing toxicity, and this should be discussed with patients.

Human papillomavirus and genital warts

Epidemiology

Genital warts are caused by infection with human papillomavirus (HPV) transmitted by skin-to-skin contact (➔ Colour plate 33). There are >100 serotypes of HPV, of which 35 preferentially infect the anogenital area. Serotypes 6 and 11 are typically responsible for warts. Infection with these types has no malignant potential.

Oncogenic types (16, 18, 31, 33, 35, and 45) may integrate with the host genome and can eventually → cervical SCC if infection is persistent and other cofactors are also present. These oncogenic types do not cause genital warts.

Genital wart virus infection is common and prevalence rates among sexually active populations may be as high as 50%. Many HPV infections are subclinical, with evidence of infection histologically or on colposcopy. HPV typing on clinical specimens is available in some countries.

Management of genital warts

Genital warts are a cosmetic problem and, although they tend to resolve spontaneously, treatment is often requested. Treatment options include the following (application of topical treatments can often be done by patient themselves):

- Cryotherapy with liquid nitrogen.
- Surgical excision.
- Laser treatment.
- Podophyllotoxin cream (0.5%) or liquid (an anti-mitotic) can be applied to accessible warts bd in cycles of 3d/wk for max. 4wks. Local irritation is a common side effect.
- Imiquimod 5% cream is a topical treatment that induces production of local cytokines and is associated with ↓ recurrence rate compared with other treatments. Apply ×1 daily, 3× per week, max. 16wks.
- Cervical warts are best treated by cryotherapy after colposcopic examination. Warts can be resistant to treatment and cause problematic recurrences in pregnancy and in HIV+ve individuals.
- Oncogenic type HPV → squamous intraepithelial lesions; best identified, treated, and followed up by colposcopy and regular cervical smears.

Prevention

Vaccines against HPV serotypes 16 and 18 (two common causes of cervical SCC) are effective in preventing the 'pre-cancerous' stage cervical intraepithelial neoplasia. Another vaccine also targets serotypes 6 and 11 (together responsible for most genital warts) (➔ Immunization, p. 853), and in addition, a 9-valent vaccine has recently become available. Some countries offer all boys and girls HPV vaccine before sexual debut (~12–14yrs). As a result of high rates of immunity in vaccinated populations and new technology, cervical cancer screening programmes are moving to HPV testing rather than cytology.

Nutrition

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Malnutrition, health, and survival

Why does malnutrition occur?

- Although infant feeding practices and food insecurity are direct causes, other causes incl. poverty, infections, chronic intestinal inflammation, and lack of care.
- Cultural risk factors incl. gender inequality, lack of exclusive breastfeeding, early introduction of complementary feeds, ↓ birth intervals, and large family size.
- ↓ breastfeeding due to fears of HIV transmission, parental sickness, and orphanhood may → malnutrition.
- Underlying factors incl. food prices, trade tariffs, political instability, ↓ political commitment, civil unrest, disasters, climate, geography, agricultural factors (e.g. soil characteristics, animal husbandry).
- Seasonal availability of cereals, fruit, or vegetables.
- Seasonal infections (e.g. diarrhoea) may also → malnutrition.
- Infections (esp. persistent diarrhoea, pertussis, measles, intestinal parasites, TB, and HIV/AIDS) may → malnutrition. Infection ↓ appetite, ↓ intake, and ↓ absorption, ↑ nutrient requirements, and ↑ urinary and intestinal losses. This → a vicious cycle of infection and malnutrition.
- Costs of treatment and follow-up can damage household finances, further ↓ intake of quality foods.

Effects of malnutrition on health and survival

- *Immunity*: malnutrition contributes to ~45% of global childhood deaths by ↑ susceptibility to common infections through ↓ barrier functions of skin, gut, and respiratory mucosa; ↓ systemic immunity; and slow tissue repair after infection. Vitamin A and Zn deficiency are important.
- *Growth and development*: dietary and genetic factors affect growth. Better diet before the age of 2yrs → lifelong improvements.
- *Organ function*: severe malnutrition → profound physiological and metabolic disturbances, with failure of normal homeostatic mechanisms (➲ Measuring nutritional status, p. 632). Nutritional deficiencies affect the eye (vitamin A), thyroid (iodine), brain (essential fatty acids, Fe), respiratory and intestinal epithelia (vitamin A and Zn), and ovaries (anorexia).
- *Pregnancy*: maternal malnutrition affects maternal health, intrauterine development, birth weight, lactation, and infant/child health.
- *Fetal programming*: intrauterine and infant malnutrition ↑ risk of adult cardiovascular disease, hypertension, diabetes, and stroke.

What are the main aspects of treatment?

- Immediately treat life-threatening complications.
- Re-establish physiology and metabolism (stabilization).
- Treat infections and comorbidities.
- Promote growth and repair.
- Address psycho-social problems and provide child stimulation.

Malnutrition with medical complications should be treated in a hospital or inpatient feeding centre. Uncomplicated moderate acute malnutrition (MAM) or severe acute malnutrition (SAM) may be treated in an out-patient/community setting with ready-to-use therapeutic food (RUTF).

See Box 16.1 for a summary. Also see http://rdcu.be/v3Kx; https://www.ennonline.net; and https://www.usaid.gov/global-health/health-areas/nutrition/technical-areas/community-based-management-acute-malnutrition

Box 16.1 Key points in malnutrition

- Most cases of severe malnutrition occur in children <5yrs. In older children or adults, suspect underlying infection (e.g. HIV, TB) or malignancy.
- Poverty and social exclusion often present; unable to afford fare to attend follow-up or buy medication.
- Modern programmes focus on early identification and community-based management of acute malnutrition before complications arise; and integrate management of SAM and MAM.
- RUTF enables effective management of uncomplicated SAM in the community.
- Complicated SAM → ↑ mortality due to ↓ immunity, metabolism, and physiology → ↓ appetite, malabsorption, and failure of homeostasis.
- Children and adults with kwashiorkor have severe physiological disturbances and ↑ mortality.
- Assessment and management require the same approach as severe microbial or metabolic illness, which often coexist.
- Usual clinical signs of infections may not be present. Sudden overwhelming sepsis may occur after clinical progress.
- Medical treatment differs from non-malnourished individuals.
- Initially, in complicated SAM, cautious feeding aims to restart metabolic processes and improve absorption by carefully replacing energy and micronutrients without overloading a fragile system.
- Even in the rehabilitation phase, children and adults remain very vulnerable; on returning home there may be poor diet and high infection risk before immunity recovers.
- Children and adults with MAM are also at ↑ risk of death.
- Health professionals have a vital advocacy role in preventing malnutrition.
- Obesity is also an increasing problem in resource-poor countries.
- Over- and undernutrition may coexist in the same household.

Measuring nutritional status

Weight and height

Weight and height measurements require equipment. They can be useful to detect wasting and stunting (Tables 16.1 and 16.2), as well as for individual monitoring over time, e.g. growth velocity.

- *Weight for height (W/H)*: weight relative to standard weight for a child of the same height. For children <2yrs, measure length (lying, W/L), rather than height. ↓ W/H = *wasting*, indicating acute malnutrition.
- *Height for age (H/A)*: height relative to the standard height for a child of the same age. ↓ H/A = *stunting*, indicating chronic malnutrition. Wasting and stunting may occur together.
- *Weight for age (W/A)*: weight relative to the standard weight for a child of the same age. ↓ W/A = *underweight*; does not distinguish acute from chronic malnutrition since a tall, thin child may be the same weight as a short, fat child of the same age. W/A is thus not used for diagnosis of acute malnutrition, but plotted over time as a useful marker of progress.

W/A, H/A, and W/H are expressed as centiles, or as *Z* scores; e.g. if weight is 2 standard deviations below mean weight of normal children of same age, *Z* score is –2 (Tables 16.1).

Mid-upper arm circumference

In children, measurement of mid-upper arm circumference (MUAC) is measured using a tape or marked plastic strip around the left upper arm (Fig. 16.1). Between ages 6mths and 5yrs, MUAC increases slowly, so simple cut-off values may be used for nutritional assessment. MUAC <115mm is equivalent to a W/H *Z* score of –3 (i.e. SAM). MUAC <125mm is equivalent to a W/H *Z* score of –2 (i.e. MAM). MUAC is much quicker and easier than calculating W/H, esp. in sick patients, and is also a good predictor of mortality. There is no need to use both MUAC and W/H.

Body mass index (BMI)

BMI assesses undernutrition or obesity among non-pregnant adults. Normal values vary with age in childhood and BMI is affected by individual variation in build and muscle bulk, so should be interpreted with this in mind. BMI = weight/(height)^2.

'Visible severe wasting' (VSW)

VSW = muscle wasting in buttocks, loss of subcutaneous fat, or prominence of bones, e.g. ribs/spine/pelvis. VSW is not sensitive, identifying mostly very severe cases of SAM. It is better to use MUAC.

Fig. 16.1 Measuring MUAC of a young child in Niger. The tape has three colours, red indicating severe acute malnutrition, yellow indicating moderate acute malnutrition, and green indicating normal nutritional status. Reproduced with permission from David di Lorenzo, Médecins Sans Frontières—Switzerland.

Table 16.1 Thresholds for malnutrition in children, adults, pregnant women, and the elderly

Age group	Severe	Moderate	At risk
MUAC			
Infants <2–5mths	<110mm*		
Children 6mths–5yrs	<115mm	115–124mm	125–135mm
Children 5–18yrs	Varies with age**		
Adults#	<160mm	160–185mm	–
Elderly#	<160mm	160–175mm	–
Pregnant/lactating women#	<185mm	185–210mm	210–230mm

Age group	Severe	Moderate	At risk
W/H Z score##			
Infants <6mths	<–3	–3 to –2	–2 to –1
Children 6mths–5yrs	<–3	–3 to –2	–2 to –1
Children 5–18yrs	<–3	–3 to –2	–2 to –1
Adults	–		
Elderly	–		

Age group	Severe	Moderate	At risk
Pregnant/lactating women	–		

Age group	Severe	Moderate	At risk
BMI			
Children 0–18yrs	Varies with age‡		
Adults	<16	16–17	17–18.5
Pregnant/lactating women	–		
Elderly	–		

* MUAC increasingly used for infants <6mths, but is still being investigated and there is no international consensus. ➲ Severe malnutrition in infants <6 months old, p. 652.

** http://www.ennonline.net/fex/54/cutoffpointsadolescentssyria and:

Girls: http://www.bmj.com/content/bmj/suppl/2017/08/03/bmj.j3423.DC1/mral036206.wf1.pdf.

Boys: http://www.bmj.com/content/bmj/suppl/2017/08/03/bmj.j3423.DC1/mral036206.wf2.pdf.

Decisions to admit are also influenced by recent weight loss or chronic illness, e.g. HIV.

See WHO charts and tables at: http://www.who.int/childgrowth/standards/en/.

‡ See WHO charts and tables at: http://www.who.int/growthref/who2007_bmi_for_age/en/.

Kwashiorkor (oedematous malnutrition) indicates severe malnutrition at any age.

Classified as:

+ mild—oedema of both feet.

++ moderate—oedema of both feet + lower legs, hands, or lower arms.

+++ severe—generalized oedema including both feet, legs, hands, arms, face.

Reference growth standards and growth charts

Table 16.2 Example W/L reference tables for boys and girls 0–2yrs

Weight-for-length GIRLS Birth to 2yrs (Z-scores)					Weight-for-length BOYS Birth to 2yrs (Z-scores)				
cm	–3 SD	–2 SD	–1 SD	Median	cm	–3 SD	–2 SD	–1 SD	Median
60.0	4.5	4.9	5.4	5.9	60.0	4.7	5.1	5.5	6.0
60.5	4.6	5.0	5.5	6.0	60.5	4.8	5.2	5.6	6.1
61.0	4.7	5.1	5.6	6.1	61.0	4.9	5.3	5.8	6.3
61.5	4.8	5.2	5.7	6.3	61.5	5.0	5.4	5.9	6.4
62.0	4.9	5.3	5.8	6.4	62.0	5.1	5.6	6.0	6.5
62.5	5.0	5.4	5.9	6.5	62.5	5.2	5.7	6.1	6.7
63.0	5.1	5.5	6.0	6.6	63.0	5.3	5.8	6.2	6.8
63.5	5.2	5.6	6.2	6.7	63.5	5.4	5.9	6.4	6.9
64.0	5.3	5.7	6.3	6.9	64.0	5.5	6.0	6.5	7.0
64.5	5.4	5.8	6.4	7.0	64.5	5.6	6.1	6.6	7.1

Weight-for-length GIRLS Birth to 2yrs (Z-scores)					Weight-for-length BOYS Birth to 2yrs (Z-scores)				
65.0	5.5	5.9	6.5	7.1	65.0	5.7	6.2	6.7	7.3
65.5	5.5	6.0	6.6	7.2	65.5	5.8	6.3	6.8	7.4
66.0	5.6	6.1	6.7	7.3	66.0	5.9	6.4	6.9	7.5
66.5	5.7	6.2	6.8	7.4	66.5	6.0	6.5	7.0	7.6
67.0	5.8	6.3	6.9	7.5	67.0	6.1	6.6	7.1	7.7
67.5	5.9	6.4	7.0	7.6	67.5	6.2	6.7	7.2	7.9
68.0	6.0	6.5	7.1	7.7	68.0	6.3	6.8	7.3	8.0
68.5	6.1	6.6	7.2	7.9	68.5	6.4	6.9	7.5	8.1
69.0	6.1	6.7	7.3	8.0	69.0	6.5	7.0	7.6	8.2
69.5	6.2	6.8	7.4	8.1	69.5	6.6	7.1	7.7	8.3
70.0	6.3	6.9	7.5	8.2	70.0	6.6	7.2	7.8	8.4
70.5	6.4	6.9	7.6	8.3	70.5	6.7	7.3	7.9	8.5
71.0	6.5	7.0	7.7	8.4	71.0	6.8	7.4	8.0	8.6
71.5	6.5	7.1	7.7	8.5	71.5	6.9	7.5	8.1	8.8
72.0	6.6	7.2	7.8	8.6	72.0	7.0	7.6	8.2	8.9
72.5	6.7	7.3	7.9	8.7	72.5	7.1	7.6	8.3	9.0
73.0	6.8	7.4	8.0	8.8	73.0	7.2	7.7	8.4	9.1
73.5	6.9	7.4	8.1	8.9	73.5	7.2	7.8	8.5	9.2
74.0	6.9	7.5	8.2	9.0	74.0	7.3	7.9	8.6	9.3
74.5	7.0	7.6	8.3	9.1	74.5	7.4	8.0	8.7	9.4
75.0	7.1	7.7	8.4	9.1	75.0	7.5	8.1	8.8	9.5

Full tables are found at: www.who.int/childgrowth/standards/en/.

Pathophysiological consequences of severe malnutrition

- *Energy*: ↓ energy intake, malabsorption, ↓ liver glycogen stores, and ↓ gluconeogenesis together → ↑ susceptibility to hypoglycaemia and hypothermia.
- *Gut*: achlorhydria, ↓ gut motility, bacterial overgrowth, villous atrophy, inflammation, and gut enzyme deficiencies ↓ digestion and ↓ absorption. Environmental enteric dysfunction (EED) is widespread in children in low-resource settings (➲ Chapter 6).
- *Liver*: ↓ protein synthesis (e.g. albumin, transferrin), ↓ detoxification, and production of abnormal metabolites of amino acids and drugs. ↑ production of acute phase proteins (e.g. CRP, ferritin).
- *Renal function*: may ↓ with inability to excrete Na^+ and phosphate.
- *Whole body Na^+ ↑ and K^+ ↓*: Na+/K+ ATPase pumps are impaired; electrolytes are not normally distributed across cell membranes.
- *Muscle wasting and diarrhoea*: → deficiencies of K+, Zn2+, Ca2+, Mg2+, Cu2+.
- ↓ *red cell mass* → unbound Fe, free radicals, and antioxidant deficiency → infections, inflammation, and cell membrane dysfunction.

Immunity

- Surface and mucosal barriers impaired → pathogen/antigen entry.
- Skin excoriation → local infection, septicaemia.
- Gut inflammation and damage → bacterial translocation, bacteraemia, ↓ immunity.
- *Cellular immunity*: thymic atrophy, ↓ cellular immunity, ↓ neutrophil function.
- *Humoral immunity*: SAM has little effect on antibody production following routine immunization. Secretory IgA is ↓.

Kwashiorkor (oedematous malnutrition)

- First described among children weaned from the breast onto a maize-based diet.
- Dietary deficiencies of energy, protein, and micronutrients are common to both kwashiorkor and marasmus. Unclear why some children develop kwashiorkor and others do not (see Box 16.2 for clinical features of kwashiorkor and marasmus).
- Oedema of kwashiorkor improves on an initial low protein diet.
- Anti-oxidant deficiencies have been postulated as possible cause of kwashiorkor. However, anti-oxidant supplements do not ↓ subsequent incidence of kwashiorkor.
- Kwashiorkor may be related to enteropathy.

Pathophysiology of micronutrient deficiencies

- ↓ intake of micronutrients → depletion of body stores → clinical signs in severe cases: xerophthalmia (vitamin A), pellagra (niacin), scurvy (vitamin C), anaemia (iron/folate/vitamin B_{12}), rickets (vitamin D/calcium), clotting abnormalities (vitamin K), and goitre (iodine).
- ↓ intake of protein, essential amino acids and minerals → ↓ growth rate or ↓ weight, usually without specific signs of deficiency.

Box 16.2 Comparisons of clinical features of marasmus and kwashiorkor

Clinical features of marasmus (Colour Plate 21)

- *Wasting*: low MUAC or W/H *Z* score.
- *Emaciated*: thin, flaccid skin ('little old man' appearance), grossly ↓ fat and muscle tissue; prominent spine, ribs, pelvis.
- *Behaviour*: alert and irritable.
- Distended abdomen due to weakened abdominal muscles and gas from small bowel bacterial overgrowth.

Clinical features of kwashiorkor

- Low or normal MUAC or W/H *Z* score.
- *Oedema*: bilateral pitting limb oedema; periorbital oedema; may be generalized.
- *Skin changes*: desquamation, often in the flexures and perineum.
- *Hair changes*: dry, thin hair that may become depigmented and appear brown, yellowy-red, or white.
- Hepatomegaly is common.
- *Behaviour*: miserable, lethargic, and apathetic with sad facies.

These clinical features may occur together: marasmic–kwashiorkor. See Colour Plate 21.

Further reading

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004825/

Clinical assessment of nutrition

History and physical examination

Look for complications, physiological dysfunction, infections, signs of specific nutrient deficiencies, underlying illness, feeding patterns, and modifiable risk factors.

History

Concurrent illness/symptoms

- Current or recent illness (diarrhoea, malaria, LRTI, etc.).
- Duration, frequency, and nature of vomiting or diarrhoea.
- Behaviour and activity changes (crying, irritable, apathy, anorexia).
- Hydration: recent sinking of eyes, time when urine was last passed.

Feeding history

- Food and fluids taken in past few days? Thirst? Appetite?
- Breastfeeding history: how long for? Mixed or exclusive breastfeeding? Is child breastfeeding now? Age complementary feeds introduced?
- Usual diet before current illness, lack of food in household or quality of food, recent change in diet.

Growth history

- Birth weight; prematurity; whether a twin.
- Review growth chart.

Other medical history

- HIV/AIDS status of child and mother.
- Development milestones reached (e.g. sitting unsupported 9mths, standing unsupported for 1–2s at 12mths).
- Immunization and vitamin A doses up to date? (➔ Chapter 21).

Family history

- Deaths of siblings or parent.
- Is the mother ill (mental or physical health) or malnourished?
- TB contact?

Physical examination

- Airway, breathing, circulation, disability, glucose (address these first).
- Appearance, pallor, behaviour, mood (apathy, irritability), conscious level, facial appearance, signs of kwashiorkor/marasmus (Fig. 16.2, Colour Plate 21).
- Fever or other signs of infection.
- Enlarged or tender liver, jaundice; abdominal distension, tenderness.
- Skin changes: desquamation, oedema, rash (e.g. post measles), exfoliation, fungal infection, cancrum oris.
- Signs of chronic disease causing 2° malnutrition: cardiac, cerebral palsy or congenital syndrome (e.g. Down's syndrome).
- Appetite test (Box 16.3).

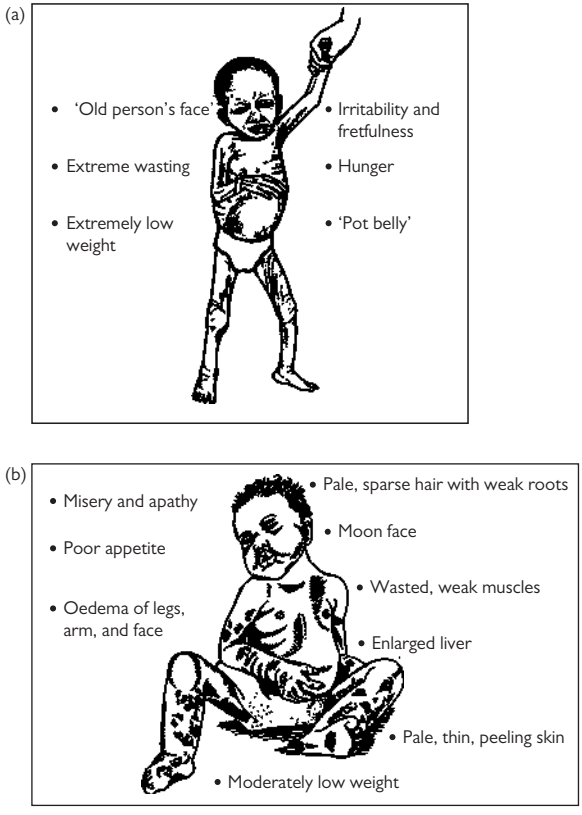

Fig. 16.2 Signs of marasmus (top) and kwashiorkor (bottom). See Colour Plate 21.

Uncomplicated or complicated malnutrition?

Children with *uncomplicated malnutrition*:

- Are alert.
- *And* have *no* respiratory distress, shock, hypoglycaemia, hypothermia, severe diarrhoea, dehydration, convulsions, or severe oedema.
- *And* have no other reason for admission to hospital (e.g. pneumonia).
- *And* pass an appetite test (Box 16.3).

Children with *complicated malnutrition* fail appetite test *or* have severe oedema *or* have signs of infection or metabolic disturbance.

Laboratory evaluation

The following are rarely available or helpful. Some are altered by inflammation:

- *Serum proteins*: e.g. albumin, transferrin.
- *Micronutrients and RBC enzymes.*
- *Markers of infection*: CRP, ESR.

Management plan

Depends on whether the child has complicated or uncomplicated malnutrition, and whether MAM or SAM. Use the algorithm in Fig. 16.3.

Box 16.3 Appetite test

Appetite is a good marker of metabolic disturbance, and whether a malnourished child needs to be admitted.

- In a quiet area, explain to the mother/carer the purpose of the test.
- The caregiver washes her hands with soap and water.
- The caregiver either offers RUTF (➲ Box 16.1, p. 631) from the packet, or puts a small amount on her finger and gives it to the child.
- If child refuses, caregiver continues to encourage child. Child must not be forced to take the RUTF.
- Child might refuse to eat the RUTF because of the strange environment—in this case the carer should take the child to a quiet place and gently encourage them.
- Offer plenty of clean water to drink from a cup while he/she is taking RUTF.
- The mother must be happy that child is eating RUTF and clinic worker should actually see child eat the RUTF.
- The child should be able to eat about a quarter of a 92g sachet.
- Any child not eating RUTF has failed and should be admitted.

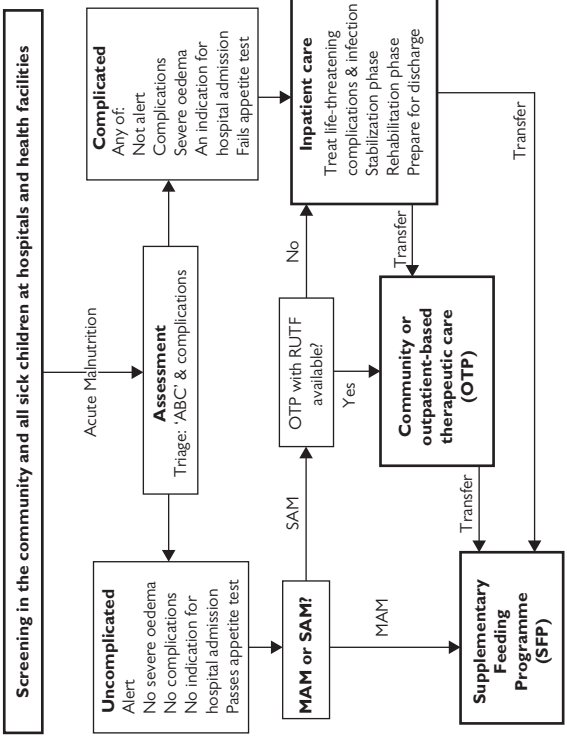

Fig. 16.3 Algorithm for categorization and management of children with malnutrition.

Medical management within inpatient therapeutic nutrition programmes

Manage life-threatening complications

See Chapter 1 for management of airway, breathing, circulation (ABC) and shock in severe malnutrition (➲ Emergency management of the sick child—ABC, p. 8). Common complications are infection, dehydration, hypothermia, hypoglycaemia, severe anaemia, and electrolyte abnormalities. See ➲ Hypoglycaemia p. 12 for management of hypoglycaemia. Other complications are discussed in the following subsections.

Severe anaemia

Transfuse if Hb <4g/dL; or 4–6g/dL with respiratory distress. If not shocked, give 10mL/kg whole blood slowly over 3h. If shocked—see ➲ Management of shock in children with severe acute malnutrition, p. 11.

Dehydration

❗ IV fluid resuscitation is controversial and may → potentially dangerous under- or overhydration. Use oral rehydration solution (ORS) designed for severely malnourished children (ReSoMal) unless there is established shock (➲ WHO defined shock, p. 7 and Management of shock in children with severe acute malnutrition, p. 11).

Dehydration may be difficult to assess as acute malnutrition may → sunken eyes and ↓ skin turgor. Assessment is best made on the basis of history or observed fluid losses. Use ReSoMal, rather than standard ORS (➲ Recipes and formulas for management of malnourished children, p. 656): give 5mL/kg orally/NG every 30min for the first 2h; aim to give 70–100mL/kg over 12h. ReSoMal can be given with F-75. Once rehydrated, continue F-75 and replace volumes lost in stool. Continue breastfeeding if possible. Reserve IV fluids for children in decompensated shock, or maintenance only in those not tolerating oral/NG fluids (with monitoring as described previously). Signs of rehydration may include return of tears, moist mouth, less sunken eyes and fontanelle, and ↑ skin turgor. Weigh daily.

Hypothermia

Rectal temp <35.5°C is a dangerous sign, associated with infection and hypoglycaemia. Change wet nappies/bedding, ensure does not get cold during washing. Provide blankets/lamps/heaters and hats (↓ heat loss), esp. at night. Encourage 'kangaroo' technique: mother lies supine with child on her chest covered by her clothes/blankets.

Infection

Bacterial sepsis

Common cause of death in severely malnourished children. Signs of infection may be absent, so give all children with complicated SAM broad-spectrum antibiotics:

- Ampicillin (50mg/kg qds IM/IV) plus gentamicin (7.5mg/kg od IM/IV); or ceftriaxone (50mg/kg od IV over 2–4min).
- Metronidazole (7.5mg/kg tds for 7d) is used in some settings if suspected protozoal (e.g. amoebiasis) or anaerobic infection.
- Continue co-trimoxazole if taken as prophylaxis in HIV infection.

- Continue IV antibiotics for at least 48h. If no signs of infection, good appetite and any oedema improving, consider change to oral amoxicillin (40mg/kg bd) to complete 7d of antibiotics.
- Severely malnourished children are highly vulnerable to hospital-acquired sepsis - if suspected, give broad spectrum IV antibiotics guided by local microbiology/guidelines or specialist advice.

Other infections

- Malaria—do blood film/malaria RDT on admission.
- UTIs are common—clean catch urine dipstick (and culture if available).
- HIV—counsel and test for HIV *at admission* for all severely malnourished children.
- Helminths—after stabilization give single dose of oral albendazole (400mg oral if >10kg; 200mg if >6mths but <10kg).
- Screen for other infections as clinically indicated—if available, consider chest X-ray, LP, blood cultures; consider TB (see later in topic).

Diarrhoea

Common causes incl. infection, osmotic load 2° feeding, lactose intolerance, premature transfer to the next feeding phase, and sepsis.

- Cohort patients and wash hands to avoid spread.
- If severe, revert to F-75 or non-milk-based feed. If possible, test stool for reducing substances (in lactose malabsorption stool pH usually <5.5).
- Check feed volumes correct—large boluses may → ↑ diarrhoea.
- Consider stool microscopy for *Cryptosporidium* or other intestinal parasites, (see Colour Plate 6) particularly if severely malnourished and HIV positive.
- Treat dysentery with antibiotics.
- Zn is already included in therapeutic feeds; no extra Zn required.

Tuberculosis

Severely malnourished children have ↑ TB risk, but clinical features are non-specific and a microbiological diagnosis is rarely possible. Consider TB in children who do not respond quickly to standard nutritional and medical treatment, and in those with a history of household TB contact (➔ Chapter 4). Cohort TB patients to avoid transmission.

Electrolyte abnormalities

↓ Na+ is common but does not reflect a deficiency in total body Na+; avoid giving too much Na+. ↓ K+ is also common, often 2° to diarrhoea, and may → cardiac arrhythmias; ↓ Mg2+ may → cardiac arrhythmias and muscle twitching. PO_4^- is often ↓.

Therapeutic feeds contain K^+, Mg2+, and other electrolytes. ReSoMal and recommended IV fluids contain less Na^+ and more K^+ than ORS and fluids used for well-nourished children.

! *Note*: a target mortality of <5% is often quoted. However, this refers to outcomes in *both* complicated and uncomplicated cases combined. Among uncomplicated cases, case fatality should be <1%. Among complicated cases, it is likely to be >5%.

Inpatient therapeutic nutrition programme

Combine therapeutic nutritional treatment with intensive medical care (➔ Medical management within inpatient therapeutic nutrition programmes, p. 642). Management of infants <6mths is covered in ➔ Severe malnutrition in infants <6 months old, p. 652. Nutritional treatment is divided into stabilization, transition, and rehabilitation phases. Treatment is the same for wasting and kwashiorkor.

Stabilization phase

Frequent, low-protein, fat, and energy feeds (F-75) with micronutrients to restart metabolic and physiological processes. This also allows oedema to begin to clear (Box 16.4).

- Give 130mL/kg F-75 daily, as 3hrly feeds (Table 16.3); continue feeding at night to prevent hypoglycaemia.
- If unable to take sufficient feed orally, give via NGT. Offer each feed by mouth and give remainder via NGT. NGT may be removed when child takes most of daily diet orally.
- Monitor vital signs at least twice daily; weigh each morning before feed; assess oedema daily.
- Give folic acid 5mg on admission.
- Vitamin A is contained in therapeutic feeds; unless there are signs of deficiency or measles, additional vitamin A is not required. If signs of vitamin A deficiency or measles, give vitamin A on days 1, 2, and 14 (➔ Vitamin A deficiency, p. 658).
- Sufficient Zn is contained in commercial therapeutic feeds for children with diarrhoea; do not give additional Zn.
- All other micronutrients are contained in *commercial* F-75.
- Do not give iron during stabilization phase as it is pro-inflammatory, oxidant and can promote infection (e.g. *Salmonella*).

Transition phase

Once appetite returns, oedema starts to clear, and medical complications treated (usually after ~3–7d), child may enter transition phase with ↑ dietary intake and close monitoring—problems can occur with ↑ dietary Na+, fluid, osmolality, and amino acids. Key components are:

- Switch to same amount of F-100 therapeutic milk and continue to feed regularly (e.g. 8 feeds in 24h).
- Gradually ↑ successive feeds by 10mL until refusal.
- Monitor vital signs at least twice daily; weigh and assess oedema daily.
- Once tolerating feeds, provided improving and not losing weight, may enter rehabilitation phase.

Note Oedematous children lose weight before starting to gain.

❗ Failure to lose oedema or gain weight is almost always because of either inadequate intake of feeds and/or infection.

Box 16.4 Therapeutic and supplementary feeding products

Milk-based products

F-75 and F-100 are specially formulated milks, commercially or locally prepared (➲ Recipes and formulas, p. 656). F-75 (75kcal and 0.9g protein/100mL) is used for cautious feeding in the stabilization phase to restart metabolic processes, ↓ oedema, and regain appetite. F-100 (100kcal and 2.9g protein/100mL) is for catch-up growth in the transition and rehabilitation phase. F-75 and F-100 contain protein, energy, and fats and commercial (but not all local) preparations contain micronutrients. They do not contain additional iron. Because of a short shelf-life, they are not suitable for use at home. Commercial F-75 and F-100 contain maltodextrin instead of sugar, which ↓ osmolarity and ↓ risk of osmotic diarrhoea.

Ready-to-use therapeutic food

RUTF is a paste based on peanuts or cereals/legumes; it is lipid, protein, energy, and micronutrient rich. RUTFs are tasty, with a nutritional composition similar to F-100 (including extra K+). RUTF is resistant to microbial contamination (unopened, it can be stored safely in tropical conditions for many months), has lower osmolarity than F-100, and micronutrients (e.g. vitamin A) are preserved. Typically, a 92g sachet = 500kcal.

RUTF should be eaten from the packet and needs no cooking. Encourage breastfeeding; other foods should not be encouraged until weight gain is established. RUTF can be used at home for uncomplicated SAM or interchangeably with F-100 in hospital. Give plenty of drinking water with RUTF. There is no RUTF equivalent of F-75: RUTF is unsuitable for the stabilization phase of complicated SAM.

RUTF can be produced locally, but commercial formulations are widely available, often supported by NGOs or UNICEF. Commercial RUTF contains maltodextrin instead of sugar, which ↓ osmolarity. Instructions for local RUTF production are on the WHO website: http://www.who.int/nutrition/topics/backgroundpapers_Local_production.pdf.

Supplementary feeds

Supplementary feeds are used to treat MAM in supplementary feeding programmes (SFPs). They typically include micronutrient-fortified, blended cereals and pulses as dry rations and vegetable oil. Local food preferences should be respected. Ready-to-use supplementary food (RUSF) is available, designed for nutritional requirements in MAM, but is expensive.

Rehabilitation phase

When appetite ↑, oedema ↓, and medical complications stable, child may enter rehabilitation phase, which aims to promote rapid growth. See Table 16.4.

- Gradually ↑ to >200mL/kg/d F-100 (=200kcal/kg/d) as 5 feeds/d.
- RUTF and F-100 are interchangeable: 20g RUTF = 100mL F100.
- Give iron 3mg/kg/d (unless using RUTF—11.5mg iron per sachet).
- Record the dietary intake.
- Give albendazole (➲ Medical management within inpatient therapeutic nutrition programmes, p. 642).

- Check temperature and clinical condition daily.
- Check weight and oedema 3 × per week.
- Promote breastfeeding.
- Encourage play therapy and physical activity to ↑ parental bonding and stimulation, speech, and motor development.
- ❗ If deterioration → ABC, complications → stabilization phase.

Preparing for discharge from inpatient care

Plan discharge in advance with the clinician, nutritionist, and the parent/carer.
Refer to an outpatient therapeutic nutrition programme (OTP) or SFP:

- Stable children may be discharged to OTP, even if they still meet criteria for SAM. However, they must pass an appetite test with RUTF (➲ Box 16.3, p. 640).
- Only children who are stable, eating well, and meet criteria for MAM may be discharged to a SFP.
- Provide locally appropriate nutrition counselling/health education.
- Refer families with serious social or parental health problems to appropriate services if available.
- Encourage regular visits to under-5s clinics, immunization, and regular vitamin A prophylaxis (3× per year).
- Immunize all children aged 9mths–15yrs against measles unless proof of previous vaccination. Re-immunize children who were immunized at <9mths.

Follow-up

- Follow-up is best at an OTP or SFP.
- If no OTP/SFP available, continue therapeutic feeding until the WHZ is >–2 or MUAC >12.5cm and oedema resolved > 2wks.
- See child after 1wk and then every 2wks to check weight/MUAC gain. After nutritional recovery child should grow at 1–2g/kg body weight/d. Check for dietary/medical reasons for poor weight gain.
- Refer child to clinic or community-based programme for monitoring 'at-risk' children; children can be referred back in case of problems.
- Children remain highly vulnerable after discharge. Advise parents/carers to bring the child to hospital if any illness or concern.

Table 16.3 Amounts of F-75 required for stabilization phase

Weight (kg)	2-hourly feed	3-hourly feed	4-hourly feed	Weight (kg)	2-hourly feed	3-hourly feed	4-hourly feed
2.0	20	30	45	6.2	70	100	135
2.2	25	35	50	6.4	70	105	140
2.4	25	40	50	6.6	75	110	145
2.6	30	45	55	6.8	75	110	150
2.8	30	45	60	7.0	70	115	155
3.0	35	50	65	7.2	80	120	160
3.2	35	55	70	7.4	80	120	160
3.4	35	55	75	7.6	85	125	165
3.6	30	60	80	7.8	85	130	170
3.8	40	60	85	8.0	90	130	175
4.1	45	65	80	8.2	90	135	180
4.2	45	70	90	8.4	90	140	185
4.4	55	70	95	8.6	95	140	190
4.6	50	75	100	8.8	95	145	195
4.8	55	80	105	9.0	100	145	200
5.0	55	80	110	9.2	100	150	200
5.2	55	85	115	9.4	105	155	205
5.4	60	90	120	9.6	105	155	200
5.6	60	90	125	9.8	110	160	215
5.8	65	95	130	10.0	110	160	220
6.0	65	100	130				

Table 16.4 Amounts of RUTF required for rehabilitation phase

Weight (kg)	92g sachets/d	92g sachets/wk
3.5–3.9	1.5	11
4.0–5.4	2	14
5.5–6.9	2.5	18
7.0–8.4	3	21
8.5–9.4	3.5	25
9.5–10.4	4	28
0.5–11.9	4.5	32
12	5	35

Outpatient therapeutic nutrition programme

The aim of an OTP is to screen and identify the severity of malnutrition and plan treatment. For uncomplicated SAM, provide medicines and therapeutic feeds, and advise patients/carers.

Treat infection (often subclinical)

- Treat all children with SAM for infection whether they have clinical signs or not. For uncomplicated SAM, give amoxicillin (40mg/kg bd po) for 5d. If child on co-trimoxazole or antiretroviral therapy, these should continue.
- Give single-dose albendazole if aged ≥6mths.
- Test all severely malnourished children for HIV.
- Diagnose and treat malaria and UTIs, URTIs, skin infections, etc.
- Ensure up to date with immunizations.
- Give vitamin A on days 1, 2, and 14 if signs of deficiency (➲ Vitamin A deficiency, p. 658).
- Additional iron and folate not needed (contained in RUTF).
- Follow up the child weekly until adequate weight gain.

Outpatient RUTF programme

The aim is to manage children with SAM at home, provided they can eat adequate amounts of RUTF.

Give sufficient RUTF to last until the next visit

- Follow up every 2wks until weight gain satisfactory (e.g. >5g/kg/d).
- Give up to 100kcal/kg body weight/d (using teaspoon equivalents of RUTF) until oedema has resolved.
- If no oedema, or oedema resolved, give 150–220kcal/kg/d.
- RUTF of 200kcal/kg/d can → a daily weight gain of up to 20g/kg body weight.
- Advise carer to feed frequently, keep child warm (esp. at night), and to return if child develops an infection or refuses RUTF.
- RUTF is sometimes shared with other children. If intake of RUTF falls to 100–150kcal/kg, daily weight gain to falls to ~5–10g/kg/d. Give cereal/legume (e.g. corn-soy blend) supplement to the family to ensure other children do not eat RUTF intended for the index child.
- Encourage breastfeeding and plenty of drinking water with RUTF.

Give nutritional guidance to improve dietary intake

- Advise extra food in convalescent phase of an illness and how to ↑ protein and micronutrient content of their diet, if possible.
- Advise on access to local programmes which ↑ food security.
- Provide a 'take home' ration of food to provide protein, energy, and micronutrients in a form that is palatable and can be stored safely without refrigeration (e.g. RUTF).
- Discharge to SFP when appropriate (MAM).
- For kwashiorkor, therapeutic feeding should continue until oedema has resolved for >2wks.

Supplementary feeding programmes

The aims of an SFP are to conduct screening; identify the severity of malnutrition; and plan treatment (refer to paediatric ward, OTP, SFP, or home). For children with MAM, SFPs provide supplementary feeds, identify complications and advise patients/carers. MAM ↑ risks of infections and development of SAM.

Food rations

Include cereals, pulses, legumes, oil, sugar, and micronutrients, e.g. corn-soy blend (➲ Outpatient RUTF programme, p. 648). In some areas, RUSF may be available. RUSF is similar to RUTF, but designed for MAM and to be used alongside other foods. RUSF is expensive.

Medical treatment

- Albendazole if aged ≥6mths and not already treated.
- Iron and folate.
- Measles immunization unless proof of previous immunization (re-immunize children who were immunized at <9mths of age).

Nutrition counselling

Advise mother or carer on providing a healthy diet using locally available/affordable foods. Make chart of foods available, rather than trying to 'educate' mothers about food components such as carbohydrates, fats, protein, etc.

Discharge criteria

- *Children age 6–59mths*: MUAC >12.5cm without oedema.
- *Children of any age*: W/H >–2 Z scores, MUAC/age >−2 Z scores.
- *Adults*: MUAC >18.5cm, or if pregnant or HIV+, MUAC >23cm.

HIV/AIDS and malnutrition

In sub-Saharan Africa, HIV can affect ~15% in community treatment programmes, and 60% in complicated SAM. Almost all severely malnourished HIV+ve children have low CD4 counts and need ART. CD4 counts are not low in severely malnourished children without HIV.

All severely malnourished children should be tested for HIV; selective testing ↑ fear and stigma. A +ve test in the child implies the mother is also HIV+ve. Benefits of making the diagnosis include appropriate treatment of OIs, co-trimoxazole prophylaxis, ART, improving mothers' health, advice on infant feeding, and prevention of future mother-to-child transmission (➲ Chapter 3).

Specific issues in HIV+ve children

- Poor dietary intake due to weakness, painful mouth (e.g. *Candida*), anorexia (due to fever/infections), and sickness of a parent/guardian (often also HIV+ve) → limited care and food provision.
- Malabsorption and chronic diarrhoea due to intestinal parasites (e.g. *Cryptosporidium*) → nutrient losses from the intestine.
- ↑ energy expenditure due to intercurrent infections → weight loss.
- Micronutrient deficiencies (including vitamin A, Zn) are common.
- Anaemia is common in HIV+ve children, usually due to chronic inflammation rather than micronutrient deficiency.

Management

- Give co-trimoxazole prophylaxis (➲ Chapter 3).
- Give stabilization therapy (➲ Inpatient therapeutic nutrition programme, p. 644).
- During rehabilitation, aim for 220kcal/kg/d.
- Manage diarrhoea; if, e.g. due to *Cryptosporidium*, it may not improve until ART is started.
- Treat infections and OIs (➲ Chapter 3).
- Refer to ART clinic; measure CD4 count if possible.
- Due to metabolic effects of ART, children should have stabilized, appetite returned, and oedema improving before starting ART.
- Failure to gain weight is common in HIV. Investigate for TB, intestinal parasitic infections, etc.
- Prevent mother-to-child transmission (➲ Prevention of mother-to-child transmission, p. 126).
- Provide healthcare for mother/carer, incl. HIV testing +/− referral for ART. A healthy mother/carer is crucial to the child's recovery.

Nutrition

See Box 16.5 for a summary of nutrition for people with HIV/AIDS.

During follow-up, ensure adequate nutrition during OIs, and best possible food and drinking water hygiene. HIV ↑↑ the case fatality of SAM. Weight gain is often slower and may not ↑ until ART started.

Box 16.5 Nutrition in people with HIV/AIDS

Good nutrition ↑ strength, and ↓ the impact of infections. HIV/AIDS patients (even when asymptomatic) should be screened for malnutrition and need ↑ food intake:

- At least the recommended daily allowance of vitamins A, B, C, E, folic acid, and minerals (e.g. selenium, Zn).
- Even more during recovery from an infection.

Nutritional education should start once a person is identified as HIV+ve. Focus on how to meet ↑ dietary needs, ↑ hygiene, and prevent OIs. Support the entire family—includes food security, hygiene, and psychosocial care.

To optimize intake

Eat small, frequent meals; make food softer. Incl. body-building food (legumes, cereal, animal products), protective foods (fruits and vegetables, fortified food), and energy foods (sugar, starch, and fat).

Problems

- *Nausea and vomiting*: eat frequent small meals, avoid fatty food.
- *Mouth sores*: avoid spicy foods; eat soft, mashed, or liquid food.
- *Anorexia*: eat frequent small meals. Time ART to minimize impact of GI side effects (e.g. nausea) on meals.

Breast feeding and HIV/AIDS

- HIV+ve mothers are usually worried about transmission during breastfeeding. Mixed breast/replacement feeding → ↑ HIV transmission vs exclusive breastfeeding or replacement feeding.
- Many mothers end up with mixed feeding because they cannot afford to sustain replacement feeding.
- Exclusive breastfeeding ↓ risks of inadequate intake and infection (contamination).
- Cow's milk is especially hazardous. Although recipes are available for modifying cow's milk for infant use, they are impractical.
- ART for mother and child ↓↓ transmission risk during breastfeeding (➲ Prevention of mother-to-child transmission, p. 126).
- WHO recommends exclusive breastfeeding up to 6mths, and partial breastfeeding to continue to at least 12mths.
- Both ART and breastfeeding are preferable to replacement or mixed feeding.
- Replacement feeding should not be used unless it is acceptable, feasible, affordable, sustainable, and safe—in resource-poor countries these criteria are *very rarely* met.

Severe malnutrition in infants <6 months old

Maternal sickness/absence, insufficient breastmilk (stress, drought, war), inappropriate alternative feeding (unsafe bottle feeding, use of cow's milk, early weaning, inappropriate attempts to avoid breastmilk transmission of HIV), +/− LBW may → SAM and illness in infants. Diagnosis of SAM <6mths is based on:

- W/L <−3 *Z* scores *or* bilateral oedema of kwashiorkor *or*
- Weight loss and too weak to suckle effectively.
- Infant MUAC being investigated—no international consensus yet.

Breastfeeding

Breastfeeding ↑ immunity, is hygienic, clean, and cheap, and there is usually a good supply. Artificial feeding risks contamination (teats, bottles, milk left standing too long, unclean water) and dilution (cost, sharing with siblings) → inadequate intake, wrong concentration, recurrent diarrhoea → malnutrition.

Illness, insecurity, anxiety, and migration, may all → ↓ breastmilk. Mothers often think they produce less breastmilk because they are themselves malnourished. Milk *quantity* is usually only reduced once maternal energy intake is very low. Maternal dehydration may → ↓ quantity. Breastmilk *quality* (esp. micronutrients) may also be affected by maternal diet. However, maternal micronutrient or calorie supplementation during breastfeeding does not improve infant outcomes. Investigate a mother's complaint that she does not have enough milk; encourage breastfeeding and support mother with hydration and nutritious food. Only use artificial feeding if no other option; mother/carer must be trained in using milk safely—and have pots, firewood, bottles, water, for hygienic preparation.

Medical treatment

Severely malnourished young infants require similar medical care to older children with severe malnutrition:

- Antibiotics (➲ Medical management within inpatient therapeutic nutrition programmes, p. 642).
- Assess signs of micronutrient deficiency.
- Examine for congenital heart disease, cleft palate, syndromes, or neurological impairment (history of birth asphyxia).
- Address mother's health needs. Maternal depression affects infant feeding and growth. Test infant for HIV.
- Domperidone is sometimes given for re-lactation, but effect on newborn outcomes unclear. The US Food and Drug Administration advises caution due to potential cardiac toxicity. It may also discourage mothers from natural ways of enhancing breast milk production.

Nutritional treatment

Aim to re-establish exclusive breastfeeding while treating the infant. There is no stabilization phase unless the infant has kwashiorkor.

- Breastfeed as often as possible to stimulate milk production.
- At least 7d one-to-one intensive re-lactation counselling and support.

- >If needed, supplement breastmilk with diluted F-100 130mL/kg/d. In kwashiorkor use F-75 (130mL/kg/d) until oedema resolving, then diluted F-100 (➲ Recipes and formulas for management of malnourished children, p. 656).
- Use a supplementary suckling technique to ↑ breastmilk production: 🔗 www.docstoc.com/docs/48486395/UNICEF-IMAM-Publication-pdf-National-Guideline-for-malnutrition.
- When infant gaining weight at 20g/kg/d, gradually ↓ diluted F-100 until gaining weight on breastmilk alone.

If no prospect of breastfeeding

Start with diluted F-100 (or F-75 if kwashiorkor) 160mL/kg/d. When stable and tolerating, gradually ↑ diluted F-100 up to 320mL/kg/d. Once gaining weight for 3 consecutive days, very gradually replace diluted F-100 with 'normal' breastmilk substitute. ↑ from 120kcal/kg/d (normal intake) to 150kcal/kg/d for extra growth until recovered.

Monitoring

Monitor weight daily. If an infant loses weight for 3 consecutive days, check amount of milk being offered (breastmilk plus therapeutic milk); rescreen for infections or medical causes of poor feeding.

Discharge

The following conditions should be met before discharge:

- Clinically well; no clinical evidence of infection.
- *Breastfed infants*: active suckling; weight velocity >5g/kg/d on breast milk alone over 3 consecutive days.
- *Non-breastfed infants*: good appetite; weight velocity >5g/kg/d; supply of breastmilk substitutes ensured; caretaker understands dangers of artificial feeding and able to prepare feeds hygienically.

Due to costs, other maternal/family commitments, concerns about cross-infection etc, some infants may be discharged without meeting these criteria. These infants need very close monitoring, advice on returning if the infant is unwell, and a means of contact.

Box 16.6 Complications of severe malnutrition in infants

- *Hypothermia*: major cause of mortality. Keep warm: skin-to-skin contact (kangaroo position); provide blankets and caps.
- *Dehydration*: use ReSoMal.
- *Anaemia*: do not give iron routinely—only give as treatment for anaemia and start after ≥14d of nutritional treatment. Give iron 2mg/kg tds po (suspension preferable) for >3mths. If Hb <5g/dL, consider blood transfusion (➲ Severe anaemia, p. 467).
- *Candidiasis*: frequent in newborns—treat with nystatin.

Pregnancy

Nutritional counselling

There is no strong evidence that ↑ energy and protein intake during pregnancy → better outcome for infants or mothers. Energy/protein supplementation does → ↓ in small babies, ↓ stillbirths and may ↓ neonatal deaths. There is no effect on prematurity or on long-term nutritional status in mothers or infants, or evidence of improved neurocognitive development.

Iron and folic acid

In pregnancy, ↓ risk of maternal anaemia, maternal death, and stillbirth. Give iron 60mg and folic acid 400 micrograms daily.

Multiple micronutrient supplementation

Antenatal multiple micronutrient supplements may ↑ survival for some neonates, esp. those born to undernourished and anaemic mothers. Benefits are greater if used early in pregnancy and adherence is good.

- Energy/protein supplementation during pregnancy is justified in malnourished women.
- Advise non-acutely malnourished pregnant women on a healthy, balanced diet.
- Avoid vitamin A, except as part of multiple micronutrients, except for overt vitamin A deficiency (➲ Vitamin A deficiency, p. 658).
- Cut-off values used for MUAC to diagnose SAM and MAM are higher than for non-pregnant adults (➲ Malnutrition, health, and survival, p. 630).

Box 16.7 Breastfeeding: key issues promoted by WHO/UNICEF

- Early discontinuation of breastfeeding → ↑ risk of death.
- Unless medically indicated, advise exclusive breastfeeding up to 6mths.
- Train healthcare staff and have a breastfeeding policy.
- Inform pregnant women about benefits of breastfeeding.
- Encourage skin-to-skin contact in the 1st hour of life.
- Show mothers how to breastfeed and how to maintain lactation, e.g. if separated from their infants.
- Promote 'rooming in': mothers and infants should remain together 24h/d wherever possible. Encourage breastfeeding on demand.
- Do not give artificial teats or pacifiers (dummies or soothers) to breastfeeding infants.
- Do not allow formula milk promotion.
- Establish breastfeeding support groups.

Nutrition in emergencies

Emergencies are situations of exceptional and widespread threats to life, health and basic subsistence that go beyond the coping capacity of individuals and communities; typically due to famine, epidemics, natural disasters, armed conflict, population displacement; exacerbated by poverty, long-term food insecurity, weak infrastructure, and endemic diseases, e.g. HIV or kala-azar (➲ Health emergencies in humanitarian crises, p. 866). Acute malnutrition (SAM and MAM) is common in emergencies, with high mortality. Outbreaks of micronutrient deficiencies occur where diet is restricted.

Current strategies are broad based including

- Nutritional surveillance, baseline data, and early warning systems.
- National food security programmes, and training on nutrition in emergencies.
- Standardized, rapid population nutrition assessments (e.g. using MUAC) to classify prevalence of malnutrition (critical >15% wasting; acceptable <5% wasting). Include infants <6mths old. Assess HIV prevalence.
- Food distribution incl. general foodstuffs, food for work, and school-based programmes.
- Targeted therapeutic and supplementary feeding with RUTF or blended dry rations with micronutrients.
- Provision of other aspects of healthcare.
- Promotion of breastfeeding, restricted use of breast milk substitutes.
- Non-food interventions, e.g. livelihood generation, agricultural improvement.
- Child protection is an important issue—needs support and referral services.
- Coordination between humanitarian agencies, health providers, social welfare institutions, and government; occasionally military.

Resources available at: 🖱 http://www.unscn.org/en/resource_portal/index.php and The Emergency Nutrition Network: 🖱 http://www.ennonline.net/.

Recipes and formulas for management of malnourished children

Electrolyte/mineral solution (EMS)

Used in the preparation of starter (F-75) and catch up (F-100) feeding formula and ReSoMal (see later in topic). Sachets are manufactured, but if not available, prepare by dissolving the ingredients listed in Table 16.5 in cool, boiled water made up to 2500mL solution. Store EMS in sterilized bottles in the fridge to ↓ deterioration. Discard if turns cloudy and make fresh each month.

If available, commercial mineral and vitamin mix is preferable as it contains all necessary micronutrients.

Nutritional rehabilitation formulas F-75 and F-100

If ready-made sachets of F-75 and F-100 are not available, prepare using ingredients listed in Table 16.6 by mixing the milk, sugar, oil, and EMS into a paste, and then slowly adding warm, boiled water to make up to 1000mL. Mix with an electric blender or hand whisk.

Commercial packets of F-75 already contain the required micronutrients and have lower osmolality because maltodextrins replace sugar.

Alternative milk ingredients

- If only whole dried milk (WDM) available, an alternative to F-75 may be prepared using 35g WDM, 100g sugar, 20g oil, 20mL EMS, and water up to 1000mL. To prepare an alternative to F-100, use 110g WDM, 50g sugar, 30g oil, 20mL EMS, and water up to 1000mL.
- If only fresh cow's milk available, another alternative to F-75 may be prepared using 300mL milk, 100g sugar, 20g oil, 20mL EMS, and water up to 1000mL. Similarly, to prepare an alternative to F-100, use 880mL milk, 75g sugar, 20mg oil, 20mL EMS, and water up to 1000mL. Fresh cow's milk carries ↑ risk of microbial contamination.

Diluted F-100 (infants only)

This is a 75% dilution of F-100 used for severely malnourished infants (➲ Severe malnutrition in infants <6 months old, p. 652). Diluted F-100 is used because infants <6mths cannot handle the solute load of full-strength F-100. It is made by adding 350mL water to 1L of prepared F-100. It supplies 75kcal/100mL, 10kcal % protein, 50kcal % fat, and is isotonic with a medium Na+ concentration. See Table 16.7.

ReSoMal

This is a low-Na+ ORS for use in severe malnutrition. For ReSoMal recipe, see Appendix 3 in: 🖉 https://www.who.int/nutrition/publications/severemalnutrition/9241546093_eng.pdf.

Table 16.5 Electrolyte/mineral solution (EMS)

EMS ingredients	Amount (g)	mol/20mL
Potassium chloride: KCl	224	24mmol
Tripotassium citrate	81	2mmol
Magnesium chloride: $MgCl_2$, $6H_2O$	76	3mmol
Zinc acetate: Zn acetate, $2H_2O$	8.2	300μmol
Copper sulphate: $CuSO_4$, $5H_2O$	1.4	45μmol
Water: make up to	2500mL	

If possible, add selenium (28mg of sodium selenate, $NaSeO_4.10H_2O$) and iodine (0.012g KI/2500mL).

Table 16.6 Nutritional rehabilitation formulas

Ingredients	F-75	F-100
Dried skimmed milk (g)	25	80
Sugar (g)	100	50
Vegetable oil (g)	27	60
Electrolyte/mineral solution (mL)*	20	20
Water: make up to (mL)	1000	1000

*Commercial mineral and vitamin mix is often available, use one 'red' scoop (6.35mg) per 2000mL of F-75 or F-100 instead of EMS.

Table 16.7 Nutritional contents of F-75 and F-100

Contents per 100mL	F-75	F-100
Energy (kcal)	75	100
Protein (g)	0.9	2.9
Lactose (g)	1.3	4.2
K^+ (mmol)	4.0	6.3
Na^+ (mmol)	0.6	1.9
Mg (mmol)	0.43	0.73
Zinc (mg)	2.0	2.3
Copper (mg)	0.25	0.25
% energy from protein	5	12
% energy from fat	32	53
Osmolality (mOsm/L)	413	41

Vitamin A deficiency

In resource-poor regions, most vitamin A is derived from breastmilk, dark green vegetables, and yellow and orange fruits. Margarine and meat (esp. liver) are also sources. Vitamin A deficiency → ↑ morbidity and mortality among children and is a preventable cause of blindness from xerophthalmia. Xerophthalmia is classified as follows:

- *Night blindness (XN)*: individual bumps into objects in poor lighting.
- *Conjunctival xerosis (X1a)*: dry conjunctiva has glazed appearance.
- *Bitot's spots (X1b)*: white foamy spots on conjunctival surface, commonly at corneoscleral junction on temporal side (Fig. 16.4).
- *Corneal xerosis (X2)*: dry cornea, associated with onset of visual impairment. Most common in children aged 2–4yrs.
- *Corneal ulceration (X3a)*: often worse in measles; central corneal ulceration may profoundly affect vision.
- *Keratomalacia (X3b)*: severe destruction of the eye with blindness; occurs especially in severe malnutrition precipitated by measles.
- *Corneal scarring (XS)*: follows healing after vitamin A replacement, often with permanent visual impairment.

Treatment

For xerophthalmia, severe malnutrition, and measles:

- Give three doses of oral vitamin A on days 1 and 2 and in week 3 (Box 16.8). High doses can fully preserve vision in stages less than X2.
- For xerophthalmia also give artificial tears and topical antibiotic eye ointment (e.g. tetracycline 1% or chloramphenicol 1%) for 10d.
- If cornea involved, close the eye and gently cover with an eye pad.

Pregnancy

Vitamin A is teratogenic at high doses—high doses are therefore contraindicated in pregnancy. Vitamin A deficiency is a severe public health problem in pregnancy if >5% of women in a population have a history of night blindness in their most recent pregnancy in the previous 3–5yrs; or if > 20% of pregnant women have a serum retinol level < 0.70mol/L; when the prevalence of night blindness is 1% or higher in children 24–59mths of age; or where the prevalence of vitamin A deficiency (serum retinol 0.70μmol/L or lower) is 20% or higher in infants and children 6–59mths of age. Country-specific information available at: http://www.who.int/vmnis/database/vitamina/en/.

Where vitamin A deficiency is a severe public health problem, give routine supplementation during pregnancy of 10,000IU daily or 25,000 weekly for a minimum of 12wks until delivery. Pregnant women with xeropthalmia should receive vitamin A 5000–10,000IU po od for 4wks. In severe xerophthalmia (acute corneal lesions), high-dose treatment can be considered, balancing the potential risks and benefits.

Prevention of vitamin A deficiency

- ↑ dietary vitamin A: carotenoids in breastmilk, spinach, carrots, sweet potatoes, mangos, papaya, milk, eggs, red palm oil, liver, fish liver oils.
- Periodic supplementation in areas of endemic vitamin A deficiency for all children aged 6mths–5yrs (including HIV-infected children), and ↑s associated with a 12% ↓ in all-cause mortality.
- WHO-recommended doses:
  - Infants 6–11mths: 100,000 IU once.
  - Children 6mths–5yrs: 200,000 IU 2–3 times/yr.

Box 16.8 Curative doses for vitamin A deficiency

- 0–6mths: 50,000IU*.
- 6–12mths: 100,000IU*.
- >1yr (including adults): 200,000IU*.
- Vitamin A deficiency in pregnant women: 10,000IU**.

* Give 3 doses of oral vitamin A (days 1 and 2, and in week 3).
** Give daily dose for >4wks, but see earlier notes.

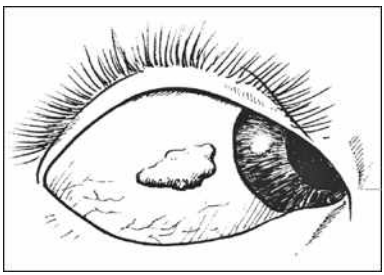

Fig. 16.4 Bitot's spot, xeropthalmia, and conjunctival xerosis. Reproduced with permission from World Health Organization, Pocket Book of Hospital Care for Children (2005), with permission of WHO.

Vitamin B_1 (thiamine) deficiency: beriberi

Thiamine is widely available, but deficiency may occur when cereals, e.g. rice, are highly milled. Deficiency may also complicate alcoholism.

Clinical syndromes

- *Dry beriberi*: symmetrical peripheral sensory and motor neuropathy: gradual onset of distal limb weakness and wasting with 'glove-and-stocking' sensory loss; foot drop and calf wasting common; affected muscles may be oedematous and contract painfully when hit; ↓ reflexes and joint position sense; ataxia +/− incontinence may develop in the later stages. Weakness and diaphragmatic paralysis → death.
- *Wet beriberi*: high-output cardiac failure + peripheral neuropathy. Typically, warm peripheries with a bounding pulse due to peripheral vasodilation. In acute, fulminant beriberi, peripheries become cold due to poor cardiac output. Death occurs due to CCF.
- *Infantile beriberi*: occurs in breastfed infants if mother thiamine deficient; important cause of infant mortality in parts of Asia. Infants typically present at 2–3mths with symptoms of progressive heart failure (not to be confused with kwashiorkor) +/− neurological signs in older infants (nystagmus, purposeless movements, ↓ consciousness, convulsions). Death due to cardio-respiratory failure.
- *Wernicke–Korsakoff syndrome*: a spectrum of neurological signs classically from chronic alcoholism; can be precipitated by infections, or carbohydrate administration (including IV glucose) before thiamine replacement. Wernicke's encephalopathy: confusion, ataxia, nystagmus and ophthalmoplegia due to haemorrhagic degeneration in the midbrain and mamillary bodies; may be reversible with urgent thiamine treatment. Chronic neurological damage → Korsakoff's syndrome characterized by short-term memory impairment and confabulation but otherwise normal cognition—recovery is rare and needs psychiatric input.

Diagnosis

Usually clinical. CXR → cardiomegaly and pulmonary oedema in cardiac beriberi. Measure blood thiamine level or erythrocyte thiamine transketolase assay (ETKA).

Management

- *Acute fulminant beriberi*: thiamine 50–100mg slowly IV tds for several days until acute symptoms improve, followed by 10mg/d orally for several weeks.
- *Chronic beriberi*: thiamine 25–100mg/d po. Limb pain improves rapidly; peripheral neuropathy may resolve in months–years.
- *Infantile beriberi*: thiamine 25–50mg given slowly IV; followed by 10mg IM daily for 1wk; then 3–5mg/d orally for 6wks. Treat mother with thiamine 10mg/d oral for 7d, then 3–5mg/d for 6wks.
- *Wernicke's encephalopathy*: IV thiamine 500mg tds for 48h followed by 250mg IV/IM for 5d in combination with other B vitamins. Consider IV vitamin B complex if locally available.

Vitamin B_2 (riboflavin) deficiency

Riboflavin is found in meat, green vegetables, milk, eggs, and wholemeal flour. Overt deficiency is uncommon. Some drugs interact with riboflavin (e.g. phenothiazines, tricyclic antidepressants).

Clinical features

Angular stomatitis, cheilosis, atrophic glossitis. There may be plugging of sebaceous glands, giving a roughened appearance to the skin, seborrhoeic and scrotal dermatitis. Normocytic-normochromic anaemia occurs because riboflavin deficiency → ↓ iron absorption.

Management Riboflavin 3–10mg po od (adults)—usually rapidly cured.

Vitamin B_3 (niacin) deficiency: pellagra

Niacin and its precursor tryptophan are found in meat, fish, nuts, fruits, and vegetables. Deficiency → pellagra; common where maize or sorghum are staples, as bioavailability of niacin in maize is low, and leucine in sorghum ↓ nicotinic acid and tryptophan metabolism. Deficiency may be prevented by dietary tryptophan, e.g. beans. Pellagra also occurs in malabsorption, isoniazid therapy, and alcoholism; may contribute to diarrhoea, depression, and skin disorders in HIV.

Clinical features

The classical triad is of dermatitis, diarrhoea, and dementia.

- *Skin*: a photosensitive, sunburn-like rash at sites exposed to sun or pressure; there may be a collar-like ring around the neck (Casal's necklace). Lesions are sensitive/inflamed, → scaly → desquamate. Atrophic patches of skin remain between the fingers; nails → brittle and atrophic.
- *Gastrointestinal*: gingival swelling +/− bleeding; raw, fissured tongue; dysphagia; villous atrophy and malabsorption; diarrhoea and nausea.
- *Neurological*: insomnia, anxiety, depression, ↓ memory, photophobia; mania or psychosis (may be permanent); pyramidal and extra-pyramidal signs; frontal reflexes. Confusion can precede death. Peripheral and cranial neuropathies also occur.
- *Eyes*: conjunctival oedema, corneal dystrophy, and lens opacities extending from the periphery to the centre.

Management Nicotinamide 300mg/d orally in divided doses until complete recovery (at least 3–4wks). Higher doses and IV therapy in severe mania.

Prevention In confirmed outbreaks, consider vitamin B complex supplements for the entire population as a short-term measure. Flour fortification with B vitamins has eliminated pellagra in the USA.

Vitamin B_6 (pyridoxine) deficiency

Clinical deficiency rare, except peripheral neuropathy during isoniazid therapy. Pyridoxine antagonists (e.g. pyrazinamide, cycloserine) may → sideroblastic anaemia. Dietary sources include meat, vegetables.

Management

Pyridoxine 50–150mg/d oral in divided doses widely used, but little evidence for efficacy. 100–400mg/d may be partially effective in idiopathic and hereditary sideroblastic anaemia. Give pyridoxine prophylaxis 10mg/d during isoniazid therapy and to malnourished alcoholics.

Toxicity Peripheral neuropathy, dermatoses, photosensitivity, and nausea reported following prolonged high-dose pyridoxine (>250mg/d). Improvement is limited even after stopping treatment.

Vitamin B_{12} deficiency

Vitamin B_{12} is available in animal products including liver, fish, meat, eggs, and dairy products, but not in vegetables. Intrinsic factor from the stomach binds vitamin B_{12} → uptake in the terminal ileum. Deficiency may be due to ↓ intake (e.g. vegans), ↓ absorption (pernicious anaemia, gastric surgery, small bowel disease, pancreatic insufficiency), or drugs (e.g. metformin, proton-pump inhibitors).

Clinical features

- *General*: angular cheilosis, glossitis; hyperpigmentation of the hands and feet is noted in some populations.
- *Macrocytic anaemia*: see ➲ Macrocytic anaemias, p. 454.
- *Subacute combined degeneration of the cord*: dorsal column and corticospinal tract degeneration → sensory and both upper and lower motor neuron signs, classically with extensor plantars but absent knee and ankle reflexes, +/− ataxia due to ↓ proprioception; pain and temperature sensation are preserved as spinothalamic tracts are not involved. May be precipitated by administration of folate to patients with combined vitamin B12 and folate deficiency.
- *Other neurological sequelae*: peripheral neuropathy, optic atrophy, dementia, neuropsychiatric symptoms, neurodevelopmental delay.

Diagnosis ↓ serum B_{12}; macrocytosis; anaemia; ↓ WBC, ↓ platelets, and ↓ reticulocytes. Tests for pernicious anaemia: parietal cell/intrinsic factor antibodies, Schilling test.

Management

Hydroxocobalamin 1mg IM 3× per week for 2wks to replenish stores, then 1mg IM every 3mths (often needed for life, if aetiology irreversible); if neurological involvement, give 1mg on alternate days until no further improvement, then 1mg every 2mths.

Vitamin C deficiency: scurvy

Vitamin C (ascorbic acid) is essential for collagen formation, ↑ iron absorption, maintaining healthy epithelial tissues (e.g. mouth, skin), and promoting wound healing. Found in fresh citrus fruit and potatoes, but easily destroyed by overcooking. Deficiency occurs when fruit and vegetables are scarce, in the elderly, and in young children (who have ↑ requirements; Box 16.9).

Clinical features

- *General*: weight loss, stiffness, weakness, painful swollen large joints.
- *Skin*: dry skin, hyperkeratosis of hair follicles, 'corkscrew hairs', bruising, perifollicular petechial haemorrhages, poor wound healing.
- *Mouth*: gingivitis, bleeding gums, dental caries, loss of teeth.
- *Anaemia*: microcytic anaemia due to iron deficiency; and/or megaloblastic anaemia as vitamin C required for folate metabolism.

Treatment Oral ascorbic acid, in divided doses per day for 2wks: infants <1mth, 50mg/d; children 1mth–4yrs, 125–250mg/d; 4–12yrs, 250–500mg/d; adults, 500mg/d.

Prevention

- Avoid overcooking vegetables; eat citrus fruit, mangos, and guavas. Supplementation if necessary (children and adults 25–75mg/d).
- Avoid artificial feeds not fortified with vitamin C.

Box 16.9 Paediatric note: scurvy in infants

Infantile scurvy typically presents at 6–12mths in premature or artificially fed infants. Erupting teeth → bleeding of the gums. Subperiosteal haemorrhages → limb pain and swelling, esp. in long bones (e.g. distal femur, proximal tibia); costochondral beading may also be palpable (scorbutic rosary). Occasionally, may be bloody diarrhoea. X-rays of long bones show epiphyseal changes and ground-glass appearance of the shafts. Microcytic and/or megaloblastic anaemia may occur.

Vitamin D deficiency: rickets and osteomalacia

Vitamin D regulates calcium homeostasis by controlling intestinal absorption and renal excretion of Ca2+, and by mobilizing Ca2+ from bone. Vitamin D is also important in cell signalling, gene expression, platelet aggregation, and host immunity (e.g. to TB).

Minimum recommended dietary intake is 400IU/d in infants, 600IU/d in children, and 600–800IU/d in adults; ↑ intake may be required. Most vitamin D3 is formed in the skin by UV light. The best food source of vitamin D is oily fish.

Deficiency may be due to dietary insufficiency, malabsorption, or lack of UV exposure (exacerbated by covering the skin, pigmentation, and lack of outdoor play). It may also be due to liver disease, renal failure, or anticonvulsant therapy (↑ vitamin D metabolism 2° to enzyme induction). Deficiency → rickets in children (Box 16.10) and osteomalacia in adults.

Clinical features

- Rickets is due to disordered bone mineralization at the growth plates, usually <2yrs. Features include:
  - Irritability, hypotonia, swollen wrists, and at older ages tender legs (may → bowed once the child starts standing).
  - Swollen costochondral junctions ('rachitic rosary'), pigeon chest, indrawing of the lower ribs (Harrison sulcus), spinal deformities, delayed fontanelle closure, bossing of the skull, and craniotabes.
  - Hypocalcaemia may → tetany and jaw, tongue or laryngeal spasm.
  - Neurodevelopmental delay esp. motor milestones.
  - Presentation depends on age.
- Osteomalacia occurs in adults, often in women or in the elderly. Presents with muscle weakness (proximal myopathy), bone pain (pelvis, ribs, femur), pathological fractures, and difficulty walking (waddling gait).
- Vitamin D deficiency → ↑ susceptibility to TB and pneumonia as well as immunological conditions (multiple sclerosis, T1DM, etc.).

Diagnosis

Diagnosis is clinical, aided by the following:

- *X-rays*: cupping and fraying of growth plates with widening of the joint space in rickets (Fig. 16.5); osteopenia, Looser's zones (partial fractures without bony displacement, e.g. of lateral scapular border, femur, or pelvis), biconcave deformity of the vertebrae.
- *Bloods*: low plasma 25-hydroxy vitamin D. Severe deficiency may → ↓ serum Ca2+, ↓ PO4–, ↑ ALP. Check U&Es for renal disease.
- *Bone scanning*: may show ↑ bone turnover, osteopenia.

Management

- Supplement with either vitamin D_2 (ergocalciferol) or vitamin D_3 (colecalciferol):
  - Infants and children: 2000IU/d or 50,000IU weekly for 6wks, followed by 400–1000IU/d (infants) or 600–1000IU/d (children) maintenance therapy.
  - Adults: 6000IU/d or 50,000 IU weekly for 8wks, followed by 1500–2000IU/d maintenance therapy.

- Give calcium (500mg/d irrespective of age/weight) in addition to vitamin D if established rickets or ↑ PTH, unless dietary sufficiency.
- Specialist regimens required if vitamin D deficiency 2° to renal disease or malabsorption.

Box 16.10 Paediatric note: calcium deficiency and rickets

- Rickets may occur due to calcium deficiency and/or vitamin D deficiency, e.g. in African children fed a maize diet low in Ca2+.
- Vitamin D deficiency may occur in infancy, due to maternal deficiency and low sunlight exposure.
- Calcium deficiency usually occurs later (may → bow legs).
- Treatment of rickets should include calcium supplementation.

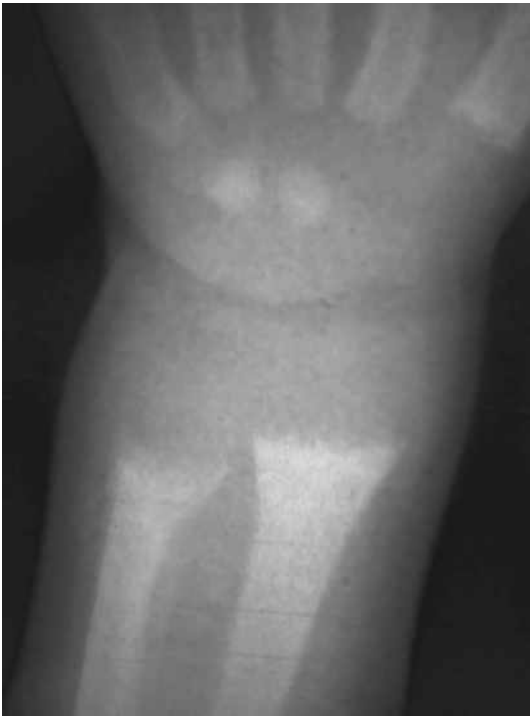

Fig. 16.5 Wrist X-ray of a 15mth child with rickets showing cupping and fraying of the distal ends of the radius and ulna.

Vitamin E (α-tocopherol) deficiency

Vitamin E deficiency develops in patients with fat malabsorption (e.g. cholestasis) and in congenital abetalipoproteinaemia. In premature infants, inadequate vitamin E stores may → haemolytic anaemia.

Clinical features Haemolytic anaemia, neuropathic disorders (ataxia, areflexia, and loss of proprioception/vibration) or skeletal myopathy.

Diagnosis ↓ serum vitamin E level.

Treatment

Few patients need treatment. Vitamin E replacement for clinical deficiency:

- Neonates: 10mg/kg oral od.
- Children (1mth–18yrs): 2–10mg/kg po od, up to 20mg/kg if required.
- Malabsorption: infants 1–12mths, 50mg od; children 1–11yrs, 100mg od; 12yrs and older, 100–200mg od; ↑ doses as required.
- β-lipoproteinaemia: neonates 100mg/kg po od; children and adults, 50–100mg/kg po od.
- Cholestasis or severe liver disease: neonates, 10mg/kg po od; child 1mth –12yrs, initially 100mg po od, adjusted according to response; up to 200mg/kg od may be required; 12yrs and older, initially 100–200mg oral od, adjusted according to response; up to 200mg/kg oral od may be required.

Vitamin K deficiency

Vitamin K is essential for production of clotting factors II, VII, IX, X, proteins C and S, and for bone growth. It is found in leafy green vegetables and is produced by intestinal bacteria. Deficiency occurs in poorly fed neonates and adults with malabsorption, and → ↑ bleeding tendency with ↑ prothrombin time. Neonates have ↓ body stores, esp. those born prematurely, and deficiency → 'haemorrhagic disease of the newborn.' This may be prevented with IM vitamin K at birth (➲ Haemorrhagic disease of the newborn, p. 479).

Treatment

For vitamin K deficiency-associated haemorrhage, replace vitamin K (children 1mth–18yrs, 250–300 micrograms/kg IV stat, up to max. 10mg; adults, 5–10mg IV).

Dietary advice suffices in most non-bleeding cases.

A note on anticoagulation

- Vitamin K is commonly administered for the reversal of warfarin.
- See ➲ Vitamin K antagonism p. 479 for further details.

Folate deficiency

Leafy green vegetables (e.g. spinach), fruits (e.g. citrus fruits and juices), and dried beans and peas are all natural sources of folate. Folate is heat labile and water soluble, so is lost in prolonged cooking or boiling. Deficiency occurs in malabsorption, in pregnancy or haemolysis, and in patients on antifolate drugs, e.g. methotrexate, phenytoin, or trimethoprim.

Clinical features Blood changes are similar to vitamin B_{12} deficiency (➲ Vitamin B_{12} deficiency, p. 454), but without neurological sequelae. Deficiency in 1st trimester pregnancy → ↑ risk of neural tube defects, IUGR, premature delivery, and LBW.

Diagnosis ↓ RBC or serum folate; macrocytic anaemia (➲ Macrocytic anaemias, p. 454).

Management

- Treat deficiency with folic acid 5mg po od for 4mths.
- ↑ doses needed in malabsorption.
- Folate can be added to flour as part of national policy.
- Folic acid from pre-conception until 12th week of pregnancy ↓ risk of neural tube defects—give 400 micrograms od if low-risk and 5mg od if high-risk of neural tube defects.
- For folate replacement in sickle cell disease, see ➲ Sickle cell disease, p. 460.

Iodine deficiency

Iodine is essential for thyroid hormone synthesis and brain development and function. Deficiency is usually due to low levels in soil and water, esp. in mountainous areas (e.g. Nepal and Bolivia) and low-lying areas where flooding washes iodine out of the soil (e.g. Bangladesh). Limited iodine availability may be exacerbated by eating brassicas (e.g. cabbage), cassava, or soya beans due to natural goitrogens in these plants. Iodine deficiency → goitre +/− hypothyroidism; it is the commonest cause of preventable mental disability ('cretinism') worldwide.

Clinical features

- *Goitre*: ↓T3/T4 production → ↑ TSH from the pituitary → thyroid enlargement. Large goitres may → recurrent laryngeal nerve compression → dysphagia and hoarseness. Patients are usually euthyroid, less commonly hypothyroid.
- *Endemic (neurologic) cretinism*: mental disability, speech and hearing deficits, strabismus, spastic diplegia, apathetic facies with thickened features. May occur due to maternal hypothyroidism even in absence of iodine deficiency.
- *Hypothyroidism* due to iodine deficiency is now rare; see ➔ Hypothyroidism, p. 496. Severe hypothyroidism → 'myxoedematous cretinism', with short stature, ataxia, and mental disability without hearing deficit.
- *Hyperthyroidism*: chronic thyroid growth may occasionally → autonomous function and toxic goitre if iodine deficiency is not severe.

Diagnosis Clinical, supported by ↑ TSH +/− ↓T4 and urinary iodine measures of dietary iodine intake.

Treatment

- Current global focus is on community-level prevention and treatment.
- Universal salt iodization as 1° prevention of iodine deficiency is the preferred method of supplementation (Box 16.11).
- Consider supplementing iodine in high-risk groups (recommended doses are listed in Table 16.8).
- Long-term dietary replacement may ↓ goitre size in pregnant women and very young children with deficiency, but is less effective for chronic goitre.
- Surgery may be required for massive goitre → compressive symptoms.

Table 16.8 WHO-recommended doses of daily and annual iodine supplementation

Population group	Daily dose of iodine supplement (micrograms/d)	Single annual dose of iodized oil supplement (mg/yr)
Pregnant women	250	400
Lactating women	250	400
Women of reproductive age (15–49yrs)	150	400
Children < 2yrs[a, b]	90	200

[a] For children 0–6mths of age, iodine supplementation should be given through breast milk. This implies that the child is exclusively breastfed and that the lactating mother received iodine supplementation as indicated previously.

[b] Assumes child is not receiving iodine fortified supplementary food

Box 16.11 Prevention of iodine deficiency

Visible goitre in >10% of the population indicates severe iodine deficiency—mass prevention should be undertaken using oral iodine (rarely, by IM injection). Iodine should also be given to pregnant women in endemic areas where <90% households use iodized salt, to prevent congenital hypothyroidism.

- *Iodized salt*: usual dose 10–50mg of iodine/kg of salt, calculated based on per capita intake of salt. Satisfactory iodization of salt can be tested using simple colour change kits based on starch/iodine interaction.
- *Iodized oil supplements* are an alternative if salt iodization is not feasible.
- Over-replacement in endemic areas may → thyrotoxicosis.

Zinc

Zinc has antioxidant properties and is essential to several proteins and enzymes, incl. those regulating gene expression. Body stores are minimal so deficiency occurs quickly, esp. in catabolic states or if ↑ intestinal losses. Zn is found in meat and fish; bioavailability from cereals is often poor because phytate binds Zn. Deficiency occurs in severe malnutrition (esp. oedematous malnutrition) and LBW infants.

Clinical features

Failure to thrive, recurrent infections, persistent diarrhoea, scaly skin lesions on the feet and buttocks (probably due to *Candida*), stunting, developmental delay. The classical acrodermatitis enteropathica rash is rare, usually due to a congenital disorder of Zn malabsorption. Plasma Zn is often ↓ in individuals but single measurements are unreliable as they ↓ in acute infection.

Treatment

Zinc 20mg/d (10mg/d in infants <6mths) ↓ duration and severity of diarrhoeal disease (including in HIV), and improves wound healing. A 10–14d course is recommended in acute diarrhoeal episodes.

Other micronutrients

Copper

Copper is important for several enzymes with antioxidant properties, and for development of collagen. It is widely available in shellfish, liver, kidney, nuts, and wholegrain cereals. Deficiency is uncommon and → osteoporosis, anaemia, neutropenia (↑ risk of infection), and neurological symptoms (cognitive impairment, ataxia, and neuropathy). Copper deficiency may be precipitated by high Zn doses → ↓ copper absorption. Menke's disease is a rare cause due to defective copper metabolism. Dietary excess (+/− genetic predisposition) is implicated in Indian childhood cirrhosis (➲ Indian Childhood Cirrhosis, p. 303).

Treatment Copper should be included in the electrolyte/mineral mix for treatment of severe malnutrition.

Selenium

Several enzymatic processes require selenium. Dietary sources incl. cereals, meat, and nuts. Deficiency occurs where cereals are grown in low-selenium soils → ↓ antioxidant activity. This may → to coronary artery disease. Selenium stimulates immunity and has been recommended as part of nutritional supplementation for HIV.

Clinical features Selenium deficiency → cardiomyopathy in parts of China where soils are deficient in selenium.

Treatment and prevention Selenium should be included in the electrolyte/mineral mix for treatment of severe malnutrition (➲ Electrolyte/mineral solution (EMS), p. 656). Fertilizers help mitigate the effect of low selenium levels in the soil.

Iron Iron deficiency is a common cause of anaemia (➲ Iron-deficiency anaemia, p. 451).

Fluoride

Fluoride is essential for mineralization of bones and teeth, and is present in the majority of foods and drinking water. Deficiency contributes to dental caries. Excess dietary fluoride may occur where the drinking water is very high in fluoride (e.g. Rift Valley in East Africa, the Punjab) → clinical fluorosis.

Clinical features

Signs of deficiency incl. dental caries and softening of long bones with deformity. Conversely, fluorosis is characterized by excess fluoride deposition in teeth and bones, with chalky discolouration of teeth enamel; spinal rigidity; restricted joint movement; ectopic mineralization of tendons, ligaments, and occasionally muscles; and ↑ bone density. Acute toxicity can → GI disturbance and if severe can → renal impairment, cardiac dysfunction, coma, and death.

Prevention Add fluoride to drinking water at source where fluoride levels low. Where fluorosis is endemic and fluoride levels in water are high, advise on alternative drinking water sources.

Obesity

People become overweight or obese because they take in more calories than they consume in metabolism and work. There is ↑ evidence for differences between individuals in appetite, fat metabolism, and metabolic responses to a meal. Obesity may also result from programming from intrauterine malnutrition, or malnutrition in the first 2yrs of life. Changes in dietary intake have been associated with ↓ physical activity. There is a global obesity epidemic, incl. in LMICs, disproportionately affecting the poor who buy cheaper, high-energy foods and high-sugar-containing drinks. Adult obesity and childhood undernutrition may coexist within households.

Obesity → ↑ risk of coronary heart disease, stroke, hypertension, T2DM, gallstones, malignancy, infections, digestive disorders, back problems, osteoarthritis, accidents, fractures, depression, and fatigue.

Diagnosis

In adults, a body mass index (BMI) >25kg/m^2 = overweight; >30 = obesity. Either BMI or W/H may be used to assess obesity in children: W/H *Z* score >+2 (>97th centile) = obesity (Measuring nutritional status, p. 632).

Management Management involves aggressive lifestyle modification focused on weight reduction; ↑ exercise; and treatment of cardiovascular risk factors. Weight loss is difficult:

- Eat foods containing more fibre and less fat or sugar. ↓ high-energy snacks—eat fruit or maize cobs; ↓ saturated fats; ↓ alcohol.
- Exercise for >20min/d at a level sufficient to raise the PR and RR.
- Be realistic and offer encouragement, not scorn.
- Advise stopping smoking and ↓ salt intake to ↓ cardiovascular risk.
- Avoid drugs to suppress appetite: evidence for these is lacking.

Metabolic syndrome

The term 'metabolic syndrome' has been given to the co-association of central (abdominal) obesity, hyperglycaemia, dyslipidaemia, and hypertension, which together identify people at high risk for developing T2DM and cardiovascular disease. Central (abdominal) obesity → insulin resistance, and to the production by adipocytes of cytokines implicated in endothelial dysfunction, dyslipidaemia, hypertension, vascular inflammation, and atherosclerotic cardiovascular disease. The prevalence of metabolic syndrome is increasing in both the industrialized and developing worlds. Other associations incl. fatty liver disease, chronic kidney disease, polycystic ovary syndrome, obstructive sleep apnoea syndrome, gout, and ↑ risk of dementia.

Chapter 17

Multisystem diseases and infections

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Differential diagnosis of fevers

Fever is a common presentation of infection (Tables 17.1 and 17.2), and, less commonly, inflammatory conditions or malignancy.

General principles of fever include:

- Fever pattern and intensity does not reliably distinguish bacterial, viral, parasitic, fungal, or non-infectious causes of fever.
- Fever is often intermittent; it may be absent at any particular point in time including in the morning, or if antipyretics (e.g. paracetamol) have been taken.
- Patients on steroids, regular antipyretics, or who are immunocompromised or neonates (0–27d) may have little or no fever.
- Rigors (uncontrollable chills/shivering) are always highly significant—most commonly caused by malaria, bacterial sepsis, or severe viral infection (e.g. influenza, dengue, Lassa fever).
- Fever may trigger febrile convulsions in children aged 6mths–5yrs (should be a diagnosis of exclusion—see ➲ p. 16).
- Drenching sweats, especially at night, are highly significant, but can occur with any cause of fever.
- Prolonged fever → weight loss due to ↓ appetite and catabolic state.

History and examination

Perform a detailed history and physical examination, considering:

- What is the age of the patient?
- Where is the site of infection?
- Which are the likely infecting organisms?
- Is this presentation unusual? Has it become more common recently? Might an epidemic be occurring?
- Is the patient immunocompromised? If so, consider possible causes for both immunocompetent and immunocompromised individuals.
- Severe malnutrition and extremes of age are associated with poorer immune responses which may → more subtle features of infection.
- Serious infections such as bacterial sepsis and malaria may have non-specific 'false localizing' symptoms, such as headache, breathlessness, vomiting, or diarrhoea.
- Viral (adenovirus, influenza) and 'atypical' bacterial (mycoplasma pneumoniae, pertussis, syphilis, TB) may be indistinguishable from 'classic' bacterial infection, especially in infants and young children.
- Carefully investigate fever in infants <3mths old; exclude meningitis with LP (fever may be only clinical sign in early meningitis).
- In the presence of localizing features, investigations are targeted towards the presumed cause, including specimens (blood, urine, CSF, etc.) for microscopy and culture, if available.
- Empiric antimicrobial treatment may be started based on a clinical diagnosis and the likely infecting organisms. Consult local guidelines for choosing antibiotics, if available.
- Be aware of risk factors (e.g. HIV, malnutrition) that ↑ risk of both severe infection and death.

Table 17.1 Common infections with localizing features

Infection syndrome	Common symptoms
Pneumonia	Breathlessness, cough, sputum, pleurisy
Pulmonary TB	Prolonged cough, haemoptysis
UTI	Urinary frequency, dysuria, haematuria, loin pain
Gastroenteritis	Vomiting and watery diarrhoea
Infective enteritis	Watery diarrhoea, central abdominal pain
Colitis/dysentery	Diarrhoea with blood and mucus, lower abdominal pain, tenesmus
Cellulitis	Red, hot skin
Septic arthritis	Painful, swollen joint
Osteomyelitis	Bone pain
Meningitis	Headache, confusion, neck stiffness
Streptococcal, EBV, diphtheria infection	Sore throat, exudate over tonsils/pharynx
TB lymphadenitis	Prominent cervical lymphadenopathy

Table 17.2 Common paediatric infections by age

Age range	Common infections
Birth to 3mths	• Bacterial sepsis • Pneumonia • Meningitis • UTI • Skin/soft tissue infection • Omphalitis • Viral (RSV; influenza; enterovirus) • Congenital infection (syphilis, CMV, *Toxoplasma*) • Gastroenteritis
3mths–5yrs	• Sepsis • Malaria • Pneumonia • Meningitis • Gastroenteritis • Septic arthritis • Osteomyelitis • Tuberculosis • Viral (chickenpox; influenza; adenovirus; measles, mumps, roseola, parvovirus)
>5yrs	• Appendicitis
>10yrs	• Sepsis • Meningitis • Osteomyelitis/septic arthritis • Cerebral abscess/subdural empyema

Fever without localizing features

Fever without localizing features may be a challenging clinical problem. Investigations (Box 17.1) should include:

- Malaria test (thick and thin blood films; malaria RDT).
- FBC (incl. differential WBC and platelet count).
- Blood culture (where available).

The importance of malaria

- Malaria is a common and important cause of fever in many settings.
- Fever is cyclical, so patient may be afebrile in a clinic.
- Asymptomatic parasitaemia is common in adults and older children in many endemic areas, due to development of partial immunity. Low-grade parasitaemia (or a +ve RDT) does not therefore prove that the fever is caused by malaria—always consider other diagnoses.
- In patients with persistent, unexplained fever, malaria testing should be repeated to exclude malaria (Chapter 2).
- Febrile patients with no visible malaria parasites (or a −ve RDT) should not routinely be treated for malaria. Exceptions may include severely ill patients unlikely to have acquired any immunity, whom it may be reasonable to treat while awaiting repeat testing.
- Artemisinins rapidly ↓ parasite counts—consider as cause of negative malaria film if prior treatment given at another health facility.
- Malaria is rare in young infants (<3mths) in endemic areas due to vertical transmission of maternal antibodies.

Blood counts in a patient with fever

WBC and platelet count may give clues to the cause (Tables 17.3 and 17.4), although they must be considered in the context of a full and careful clinical assessment of the patient.

Treatment of fever of unknown cause

Quite commonly, a definitive diagnosis cannot be made at the initial clinical assessment. Management then depends on the most likely diagnoses, how severely ill the patient is, and the available resources. Patients judged to be (or at risk of becoming) seriously unwell should be given 'best-guess' empirical antimicrobial therapy, using local guidelines if they exist. Consider admission to hospital if serious illness or concern. In time, diagnosis is likely to become apparent, particularly if patient is regularly reassessed.

Persistent fever despite antimicrobial therapy

Depending on the infection site, severity, and type, fever may take hours to days to resolve. Common causes of prolonged fever include:

- Poor source control (e.g. presence of collection/abscess).
- Antimicrobial failure—infecting organism(s) not susceptible.
- Inadequate drug concentration at site of infection—consider dose, absorption, and penetration into special sites (e.g. CSF, abscesses).
- Non-adherence or inadequate provision of antibiotics.
- Non-infectious causes of fever (including drug fever).

Table 17.3 Causes of a raised WBC (leukocytosis)—if total WBC ↑, look at the differential WBC count

Differential WBC	Common or important causes
Neutrophilia*	Bacterial infections (focal infections, sepsis, abscess, leptospirosis, borreliosis); amoebic liver abscess
Lymphocytosis	Infectious mononucleosis (EBV), pertussis, brucellosis, leukaemia
Eosinophilia	Invasive worm infections (e.g. schistosomiasis), TB

* Bacterial infections in neonates may cause neutropenia. Neutropenia may also pre-exist in infants and young children, pre-disposing to bacterial infection (e.g. congenital neutropenia; neonatal alloimmune neutropenia).

Table 17.4 Causes of fever with a normal WBC—if total WBC normal or low, look at the platelet count

Platelet count	Common or important causes
Normal	Viral infections (incl. the prodrome of acute viral hepatitis), typhoid, rickettsial infection Early bacterial infection
Low	Malaria, dengue, and other viral infections, HIV Bacterial sepsis (esp. Gram −ve infections)

Box 17.1 Investigations for fever of unknown source in children <3mths

- FBC, CRP if available.
- Urine for urinalysis, microscopy/culture.
- Blood culture.
- LP (CSF for microscopy and culture).
- CXR (even in absence of clinical signs).
- Syphilis serology (e.g. VDRL) if any signs of congenital syphilis or maternal syphilis status not known.

Sepsis

Sepsis is a syndrome of life-threatening organ dysfunction caused by infection. Bacterial infections are the commonest cause; other serious infections (e.g. falciparum malaria, Lassa fever) can cause an identical clinical syndrome. Some non-infectious insults may also → a similar clinical syndrome (e.g. pancreatitis, chemical toxins, burns, leukaemia). 2° bacterial sepsis may complicate other infections, such as malaria and severe viral infections (e.g. influenza).

Clinical features

- Clinical features of sepsis reflect the focus of infection, the systemic inflammatory response, and organ dysfunction.
- Symptoms and signs vary considerably depending on the aetiology, focus, severity, and host factors, and may be subtle in very young children (see Box 17.2 for signs of possible serious bacterial infection), the elderly, and the immunocompromised.
- Septic shock occurs when severe sepsis leads to circulatory failure and metabolic abnormalities (e.g. ↑ lactate) despite adequate fluid resuscitation, and carries a case fatality risk of >40%.

Sepsis definitions

Various definitions have been proposed, including presence of a systemic inflammatory response syndrome (SIRS) +/− organ dysfunction; and the Sepsis-3 definitions published by an international critical care task force.[1] All definitions require evidence of both infection and severe illness; all are imperfect. A pragmatic definition of sepsis is therefore 'bad (usually bacterial) infection'. Examples of severe illness ('badness') include acute confusion, hypoxia, respiratory distress, hypoperfusion, poor urine output, AKI, hepatic dysfunction, ↑ lactate, ↓ platelets, coagulopathy, etc.

Management

Sepsis matters because early diagnosis and rapid treatment of bad infections saves lives. Key components of treatment are:

- *Prompt, appropriate antimicrobial therapy* (ideally give within 1h, after blood cultures; refer to local guidelines, if available).
- Fluid resuscitation, guided by serial clinical assessments +/− lactate.
- Blood cultures (+/− other cultures as clinically appropriate).
- Regular monitoring of vital signs and urine output.
- Supportive care as indicated (e.g. vasopressors, mechanical ventilation, haemofiltration, IV hydrocortisone).

1 Singer M et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). J Am Med Assoc 2016;315:801–10.

Box 17.2 Neonatal and infant sepsis

Neonatal sepsis (Also see ➲ Sick child p. 18.)

- *Early neonatal sepsis* (onset <72h of birth) is typically due to ascending infection of maternal colonizing bacteria or infection at time of delivery (e.g. group B streptococci, *Escherichia coli*).
- *Late neonatal sepsis* (onset >72h of age) is typically due to *Staphylococcus aureus* or Gram −ve bacteria acquired from the hospital or community environment.

Sepsis in young infants (Also see ➲ Sick child p. 18.)

- Sepsis in babies <3mths can be difficult to diagnose as clinical signs are non-specific.
- Severe infection (including bloodstream infection, pneumonia, and meningitis) may present with limited clinical signs.
- WHO recommends using signs of possible serious bacterial infection (PSBI) to identify infants at risk of serious infection, to guide community management and referral.

PSBI criteria

- Temperature <35.5°C or >37.5°C.
- Lethargy (movement only when stimulated).
- Convulsions.
- Fast breathing (>60 breaths/min) or nasal flaring.
- Severe chest wall indrawing.
- Abdominal distension or refusal to feed.

Cancer

Cancer is an increasingly important cause of mortality in resource-poor countries. The global burden of cancer is likely to ↑ markedly in the next 20 years and most of the ↑ will come from resource-poor countries (globally, 1 in 5 men and 1 in 6 women will develop cancer in their lifetime). Populations are expanding and ageing, tobacco consumption is ↑, diets and lifestyle are changing to a 'westernized' pattern, and prevention of certain viral-related cancers is possible. ~60% of global cancer occurs in resource-poor countries; prevention and screening programmes, stage at diagnosis, and accessibility of therapy all affect incidence of cancer and its mortality.

There is wide geographical variation in the prevalence of some cancers. Lung cancer is the most common cancer worldwide, followed by breast, colorectal, prostate, and stomach. Cervix uteri cancer (in low-resource countries esp. sub-Saharan Africa), liver, and oesophagus are also common.

Cancer requires early intervention for therapy to be effective. Bearing this in mind, basic rules include:

- Suspect cancer in any unexplained illness, esp. in the elderly.
- Attempt to make a histological or cytological diagnosis as soon as feasible.
- Once diagnosed, patients should start a planned regimen of treatment, including symptom control, within days, not weeks (Box 17.3). Tumours grow exponentially and there is no reason to delay.

Signs and symptoms common to many forms of cancer

These may be due to a local effect of the tumour, to obstructive symptoms (e.g. biliary tract, urinary tract, airways, bowel, and lymphatics) and distant effects (e.g. paraneoplastic syndromes).

- *Pain*: due to direct effect of tumour (e.g. infiltration of nerves or compression), or metastatic spread to the bones or other organs. Any patient with unexplained persistent pain should be suspected of having malignant disease. Treatment may also → pain.
- *Weight loss*: due to involvement of GI tract (obstruction, metastatic liver involvement), anorexia, or general cachexia due to a catabolic state. This may be ↑ by treatment.
- *Tumour mass*: enables early diagnosis by biopsy (incisional or excisional); this may be part of the treatment.
- *Fever*: while normally caused by superimposed infection, fever itself may be a feature of cancers (e.g. lymphomas, renal carcinoma, and tumours metastasizing to the liver). Frequently occurs as drenching night sweats, without rigors.
- *Anaemia*: normocytic normochromic (sometimes hypochromic, microcytic if due to occult bleeding), malabsorption, or anaemia of chronic disease.
- *Hypercalcaemia*: occurs in 10–30% of cancers and is due to ↑ osteoclastic bone resorption associated with metastases to the skeleton and/or to paraneoplastic syndromes.

Paraneoplastic syndromes

These occur in ~15% of tumours, may pre-date the actual cancer diagnosis, and are due to tumour-derived cytokines or hormones, or to a tumour-induced immune response cross-reacting with normal tissue. The range includes endocrine, neurological, dermatological, musculoskeletal, haematological, and occasionally renal and GI syndromes. Paraneoplastic symptoms often improve on therapy of the cancer but the prognosis is highly variable. Most neurological problems are due to metastases, and most endocrine problems are due to endocrine tumours themselves, not paraneoplastic syndromes.

Box 17.3 WHO performance status

This is useful for grading the status of cancer patients and determining prognosis.

- 0 Able to carry out normal activity without restriction.
- 1 Restricted in physically strenuous activity, but walking about and able to carry out light work.
- 2 Walking about and capable of self-care, but unable to carry out any work; up and about >50% of waking hours.
- 3 Capable of self-care; confined to bed or chair >50% of waking hours.
- 4 Completely disabled; cannot carry out self-care; totally confined to bed or chair.
- 5 Death.

Further reading

Website: http://www.inctr.org/about/develop.shtml.

General rules of cancer management

Whenever you see a patient with cancer, consider the following points:

Could the patient have neutropenia?

Infection in a neutropenic patient often presents suddenly with sepsis, but without localizing features, and cultures are usually –ve. Neutropenia commonly follows chemotherapy. Bacterial flora from the mouth, digestive tract, respiratory tract, or skin are usually responsible, and indwelling lines and catheters may be the source; fungal infection is also possible. Any cancer patient who is feeling 'run down' and especially with a fever must have their WBC and differential count checked immediately and not be sent home. Such patients can deteriorate quickly and demise within hours.

Could the patient have hypercalcaemia?

Unlike 1° parathyroid disease, the onset is rapid and there are none of the classical 'stones, bones, or groans'. Instead, clinical features include: polyuria, thirst, confusion, fatigue, coma. Treatment of hypercalcaemia → marked improvement in the patient's condition (Box 17.4).

Is patient's pain controlled?

See Box 17.5. It may be necessary to use morphine. The following regimen is useful:

- Give morphine 10mg 4hrly at 07.00, 11.00, hours, etc., until 23.00, at which point give a double dose so that the 03.00 dose can be missed out, offering the chance of a good night's sleep.
- If pain breaks through, give an extra dose of morphine 10mg (even if the next 4hrly dose is only 10min away), continuing other doses as normal.
- As more breakthrough doses are required, ↑ regular 4hrly dose (e.g. to 20mg).
- If using long-acting morphine (e.g. MST® 80mg bd), take total daily dose (160mg) and divide by six doses to give size of the IV morphine dose to use for breakthroughs—here 160/6 = ~25mg).

Could the patient have early cord compression?

Ask:

- Can you walk?
- When was the last time you walked?
- Have you been incontinent of urine and/or faeces?
- Do a neurological exam including anal tone and sacral sensation, and check for a palpable bladder.
- Missing spinal cord compression may → patient spending their last few weeks or months in a miserable paraplegic state.

Box 17.4 Hypercalcaemia

- Rehydrate with 0.9% saline IV (e.g. 4–6L in 24h depending on hydration status).
- Once rehydrated consider forced saline diuresis: continue 0.9% saline infusion and use IV or oral furosemide 40mg if fluid overload is a potential risk.
- IV bisphosphonate infusion (e.g. zoledronic acid, pamidronate) to ↓ Ca^{2+} (max. effect at 4–7d). May need to be repeated, adjust dose with renal dysfunction. Other options exist if no response to bisphosphonates (e.g. denosumab, calcitonin). Dose varies according to serum Ca^{2+} level.
- Steroids may help in some conditions (e.g. sarcoidosis, malignancy).
- If possible, treat the underlying cause.

Box 17.5 Management of acute pain in hospital

- Effective relief can be achieved with oral non-opioids and NSAIDs. Ibuprofen 400mg is very effective and is associated with fewer GI bleeds than some other NSAIDs. Also effective are paracetamol 1g and paracetamol combined with codeine.
- Initial management of moderate pain (e.g. in post-surgical patients) should ideally be an oral NSAID, such as ibuprofen, supplemented if necessary with paracetamol. In the elderly, paracetamol may be preferred, although it is less effective. There is no evidence that parenteral is more beneficial than oral administration.
- Opioids are the first-choice treatment for severe acute pain. Additional, often smaller doses can be given if the patient is still in pain and you are sure that all the previous dose has been delivered and absorbed. Repeat doses can be given 5min after IV injection, 1h after IM or SC injection, and 90min after an oral dose. The route of administration can be changed to achieve faster control if there is no response to the repeated dose.
- Titrate opioids against degree of pain relief. Inadequate pain control results from too little drug, too long dosing intervals, too little attention being paid to the patient, or too much reliance on rigid regimens.
- Morphine is the most appropriate opioid and it is popular among pain specialists. Its analgesia lasts a reliable 4h and is easier to titrate than opioids with a longer half-life. Set up a 4hrly regimen which prevents the occurrence of pain (see 'Is patient's pain controlled?').
- As the pain ↓, the patient can be switched to ibuprofen and paracetamol. Supplementation of morphine with an NSAID if appropriate, may allow ↓ morphine dose.
- Remember to manage possible constipation resulting from opioid use.
- See Fig. 17.1.

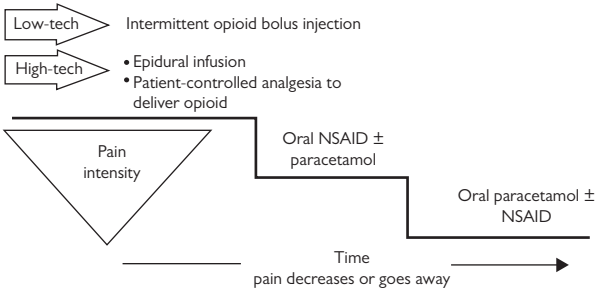

Fig. 17.1 Overview of the management of acute severe pain.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory condition of unknown cause that primarily involves joints. It is associated with disability, accelerated atherosclerosis, and ↑ mortality. Lack of treatment and poor response to treatment → permanent joint destruction and deformity. Onset usually in the 3rd to 5th decade and RA affects women 2–3× more frequently than men.

Clinical features

Symptoms Joint pain, swelling, and morning stiffness.

Clinical signs Usually chronic symmetrical joint swelling (often proximal interphalangeal (PIP), metacarpophalangeal (MCP), metatarsophalangeal (MTP), wrists, knees; affects the cervical but not the lumbar spine.

Extra-articular disease

Anaemia of chronic disease, subcutaneous nodules (usually extensor), fatigue, pleuropericarditis, myocarditis, lymphadenopathy, nerve entrapment (e.g. carpal tunnel syndrome), mononeuritis multiplex, splenomegaly, episcleritis, scleritis, Sjögren's syndrome, interstitial lung disease, vasculitis, and coronary artery disease.

Complications

Patients with long-standing RA and poor disease control may → irreversible joint damage and deformity, ↓ functional capacity, and atlanto-axial instability/subluxation. Premature death is mainly attributed to comorbid conditions such as atherosclerosis and infection.

Diagnosis

Primarily by history and physical examination. There is no definitive test (Box 17.6). The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have proposed classification criteria for patients with at least one joint with definite clinical synovitis not better explained by other disease (Box 17.7).

X-rays Affected joints may show typical changes (soft tissue swelling, symmetric joint space narrowing, bone erosions, and deformities).

Immunology

Rheumatoid factor (RhF) is +ve in ~80% (false +ve in 5% of healthy people, more often in old age, chronic infections, liver disease, fibrotic lung disease, and other rheumatic diseases). Anti-citrullinated peptide antibodies (ACPA) and RhF have similar sensitivity, but ACPA are more specific (95%).

Management

- *Non-pharmacologic*: patient education, aerobic and resistance exercise, physical and occupational therapy, smoking cessation.
- *Pharmacologic*: conventional and biologic disease-modifying antirheumatic drugs (DMARDs) are critical to prevent permanent damage. Conventional DMARDs should be prescribed as early as possible

and monitoring for drug toxicity is needed (Table 17.5); they are used alone or in combination for disease control. Most widely used are methotrexate, leflunomide, sulfasalazine, and antimalarials (chloroquine and hydroxychloroquine). A common combination is methotrexate + sulfasalazine + hydroxychloroquine. Biologic agents include anti-TNF drugs (infliximab, etanercept, adalimumab, golimumab, or certolizumab pegol), anti-CD-20 (rituximab), CTLA-4 Ig (abatacept), anti-IL-6 (tocilizumab), and anti-Janus kinase (tofacitinib—a new oral small molecule). All biologic agents and tofacitinib are extremely expensive. Rarely used DMARDs include gold salts, minocycline, ciclosporin and azathioprine. Treatment target is remission or minimal disease activity.

- *Oral NSAIDs*: they only provide symptomatic relief and do not affect outcome, and if used, should always be used with DMARDs.
- *Corticosteroids*: can be used orally in low doses (equivalent to <7.5mg of prednisolone/d) or as intra-articular injections. If steroids are used, it should be in low doses, in combination with a DMARD, and with a plan to slowly taper to lowest dose of steroid required.
- *Surgery*: for deformity, loss of function, and complications.

Contraindications to drugs for RA

- *NSAIDs*: GI bleed, peptic ulcer; if past history of GI bleed or ulcer and NSAID required, combine with a PPI (e.g. omeprazole). Caution with hypertension, IHD.
- *Methotrexate*: pregnancy, elevated creatinine, alcohol use, liver disease, abnormal LFTs, HIV, HBV, HCV.
- *Sulfasalazine*: allergy to sulfas, G6PD deficiency.

Box 17.6 Differential diagnosis of RA

- *Acute viral polyarthritis*: caused by chikungunya, hepatitis B and C, rubella.
- *Parvovirus*: self-limited (weeks); history of rash, IgM viral antibodies.
- *Connective tissue diseases*: symmetric polyarthritis without joint deformities. Look for other multisystemic features (e.g. SLE).
- *Septic arthritis*: usually acute monoarthritis. Immediate joint aspirate (for Gram stain and culture) and antibiotics are required to prevent permanent joint damage.
- *Fibromyalgia*: diffuse pain without inflammation. Insomnia and fatigue are common features.
- *Reactive arthritis*: asymmetric oligoarthritis, sausage digits. Look for urethritis, conjunctivitis, and history of enteric infection.
- *Gout/pseudogout*: acute attacks. In gout, monoarthritis of the first MTP joint is common. Definitive diagnosis made by finding crystals in synovial fluid.
- Osteoarthritis (➲ Osteoarthritis, p. 688).
- Paraneoplastic syndromes.
- HIV-associated arthritis.

Box 17.7 2010 ACR/EULAR classification criteria for RA

Classification is based on a score of at least 6 (of possible 10 points).

- Number and site of involved joints:
  - 2–10 large joints = 1 point.
  - 1–3 small joints = 2 points.
  - 4–10 small joints = 3 points.
  - >10 joints (at least 1 small joint) = 5 points.
- Serological abnormality (RhF or ACPA):
  - Low +ve RhF or ACPA = 2 points.
  - High +ve RhF or ACPA = 3 points.
- *Elevated acute phase reactant*: abnormal CRP or abnormal ESR = 1 point.
- Symptom duration 6wks = 1 point.

Table 17.5 ACR recommendations for monitoring of drugs commonly used to treat RA

Drug (usual doses)	Monitoring
Methotrexate (15–25mg once a week)	FBC, LFTs, albumin, creatinine 2–4wks for the first 3mths or after dose increase, then every 8–12wks
Hydroxychloroquine (400mg od)	Fundoscopy and visual fields every 12mths
Sulfasalazine (max. 3g per day)	FBC 2–4wkly for for the first 3mths or after dose increase, then every 8–12wks

Osteoarthritis

Osteoarthritis (OA) is a chronic, non-inflammatory arthropathy that can be idiopathic or 2° to trauma or other conditions.

Symptoms

Non-inflammatory joint pain (Box 17.8). The knees, hips, and distal interphalangeal (DIP) joints are most commonly affected. If unusual joints are involved (elbows, ankles, MCPs) look for 2° causes: previous trauma, haemochromatosis, Wilson's disease, or reconsider diagnosis (could be RA).

Clinical signs Bony swelling, crepitus.

X-ray findings Non-uniform joint space narrowing, osteophytes, and juxta-articular osteosclerosis.

Diagnosis By history and physical exam.

Management

- Non-pharmacological: patient education (↓ weight if obese, exercise to strengthen muscles around affected joint), physical and occupational therapy.
- Analgesia: paracetamol +/– NSAID +/– codeine (avoid narcotics if possible).
- Intra-articular hyaluronans (limited evidence of efficacy).
- Intra-articular glucocorticoids.
- Topical NSAIDs.
- Duloxetine.
- Surgery including joint replacement.

Box 17.8 Characteristics of joint pain and type of arthritis

Inflammatory, e.g. RA	*Non-inflammatory, e.g. OA*
• Pain ↓ with activity.	• Pain ↑ by activity.
• Worse in the morning.	• Worse at night.
• Morning stiffness >60min.	• Morning stiffness <30min.
• Systemic features: sometimes.	• Systemic features: absent.
• Soft swelling (effusion).	• Hard swelling ('bony').
• Sometimes erythema.	• No erythema.
• Sometimes warmth.	• No warmth.

Systemic lupus erythematosus

Multisystem chronic inflammatory disease, characterized by facial rash, photosensitivity, alopecia, cytopenias, nephritis, serositis, non-erosive arthritis, CNS involvement, vasculitis, and fever. Aetiology unknown. Women affected 7–15× more often than men; peak incidence 15–40yrs of age. It is associated with premature mortality. Causes of death include infections and disease activity (particularly renal) in early phases of the disease, and atherosclerosis in the long term (➲ Connective tissue diseases, p. 560, for details on cutaneous lupus erythematosus). See Box 17.10 for markers of poor prognosis.

Clinical features

- *General*: fever, fatigue, ↓ weight, Raynaud's phenomenon.
- *Joints*: arthralgia/arthritis (similar to RA, but usually non-erosive).
- *Mucocutaneous*: malar rash, photosensitivity, discoid lupus, purpura, alopecia, livedo reticularis, mouth ulcers.
- *Renal*: nephritic or nephrotic syndrome; renal failure.
- *Neurological*: cognitive defects, psychosis, seizures.
- *Serositis*: pleural and pericardial effusion.
- *Pulmonary*: pneumonitis, fibrosis, bronchiolitis, shrinking lung syndrome.
- *Cardiovascular*: hypertension, pericarditis, sterile (Libman–Sacks) endocarditis, myocarditis, coronary artery disease.
- *Blood*: normocytic anaemia, haemolysis (Coombs +ve), leukopenia, thrombocytopenia.
- *Thrombosis and miscarriage*: may be part of the antiphospholipid antibody syndrome.

Laboratory tests

Several autoantibodies that react with the cell nucleus are a feature of SLE. Antinuclear antibodies (ANAs) are +ve in >98% of patients. However, ANAs are not specific; patients with other rheumatic conditions or chronic diseases, and 5% of normal subjects can have +ve ANAs. Anti-double-stranded DNA and particularly anti-Smith (anti-Sm) antibodies are more specific but less sensitive. Other autoantibodies sometimes present are anti-Ro, anti-La, anti-RNP, and antiphospholipid antibodies. Patients can have low complement levels.

Diagnosis

The Systemic Lupus International Collaborating Clinics classification criteria for SLE are given in Box 17.9.

Management of SLE

- *Education*: avoid sun, sunscreen, hat, long sleeves, smoking cessation, prevent atherosclerotic disease.
- *NSAIDS*: useful for musculoskeletal symptoms and serositis.
- *Antimalarials (chloroquine/hydroxychloroquine)*: effective for skin and musculoskeletal symptoms; prevent renal and CNS flares, ↓ risk of thrombosis.
- *Systemic corticosteroids*: prednisolone <0.5mg/kg for moderate disease; higher doses (1mg/kg) for severe or life-threatening disease, e.g. renal disease, pneumonitis, severe cytopenias, or CNS lupus. Consider high-dose IV methylprednisolone 1g boluses for severely ill patients.

Box 17.9 The Systemic Lupus International Collaborating Clinics classification criteria

Four or more, at least one clinical and one immunologic criterion *or* biopsy proven lupus nephritis required:

Clinical

- Acute cutaneous lupus.
- Chronic cutaneous lupus.
- Non-scarring alopecia.
- Oral or nasal ulcers.
- Arthritis in two or more joints *or* pain in two more joints and morning stiffness for at least 30min.
- Serositis.
- Renal involvement: proteinuria (>0.5g/d) or RBC casts.
- Neurological disorders: seizures, psychosis, mononeuritis multiplex*, myelitis, peripheral or cranial neuropathy*, or acute confusion*.
- Haemolytic anaemia.
- Leukopenia*.
- Lymphopenia.
- Thrombocytopenia.

Immunologic

- ANA.
- Anti-double-stranded DNA.
- Anti-Sm.
- Antiphospholipid.
- Low complement.
- Direct Coombs' test.

* In the absence of other known causes.

- Corticosteroids should be tapered early according to response; combine with steroid-sparing agents to minimize steroid side effects.
- *Cyclophosphamide*: for severe SLE including proliferative lupus nephritis, vasculitis, CNS involvement, and alveolar haemorrhage.
- *Mycophenolate mofetil*: for lupus nephritis; may be as effective as cyclophosphamide with less adverse events.
- *Azathioprine*: as a steroid-sparing agent.
- *Methotrexate or leflunomide*: for arthritis.
- *Others*: chlorambucil, ciclosporin, and expensive biologic agents—rituximab (anti-CD20 antibody) and belimumab (antibody that binds to soluble B-lymphocyte stimulator).
- *Anticoagulation*: for the antiphospholipid syndrome.
- *Manage comorbidities*: such as hypertension, diabetes, osteoporosis, and heart disease.

Box 17.10 Markers of poor prognosis in patients with SLE

- Diffuse proliferative renal disease.
- Hypertension.
- Male sex.
- Lower socioeconomic and education status.
- Black and Hispanic ethnicity.
- Antiphospholipid antibodies.
- Disease activity involving multiple organs.
- Renal failure.

Further reading

Useful website: http://www.hopkins-arthritis.org/.

Typhoid and paratyphoid fevers

Also called enteric fever, these conditions follow infection with *Salmonella enterica* (*S. enterica* serovar Typhi (typhoid); or *S. enterica* serovars Paratyphi A, B and occasionally C (paratyphoid)). Endemic and important causes of morbidity across developing world. Typhoid and paratyphoid A are most severe; paratyphoid B mildest, with paratyphoid C falling somewhere in between.

Transmission

Via ingestion of food or water contaminated by infected human faeces (or occasionally, infected urine). Gastric acid is protective so ↓ acid production (e.g. due to PPIs) → ↑ susceptibility to infection. Faecal shedding occurs during acute illness, convalescence, and chronically from asymptomatic gall bladder infection.

Pathophysiology

Following ingestion, bacteria survive gastric acid barrier, then penetrate ileal wall, probably through M-cells, and pass to mesenteric lymph nodes. Following 1° multiplication in mesenteric lymph nodes, bacteria then infect cells of the reticuloendothelial system where further multiplication occurs → 2° bacteraemia, infection of multiple organs, and clinical illness. If untreated, >10% die from overwhelming sepsis or 2° organ involvement, particularly encephalopathy, toxic myocarditis, GI haemorrhage, and/or perforation and peritonitis.

Clinical features

Incubation period 10–20d; untreated illness typically lasts 4wks (may be longer in severe infections and shorter in mild cases).

- *1st week*: non-specific symptoms—malaise, headache, rising remitting fever, mild cough, constipation or mild diarrhoea, vomiting, abdominal pain.
- *2nd week*: patient becomes 'toxic' and apathetic; often mentally dull (e.g. slow response to questions) or occasionally psychotic (e.g. an agitated, febrile patient admitted to psychiatric ward); sustained high temperature with relative bradycardia; distended abdomen; enlarged liver and/or spleen; rose spots (2–4mm pink papules on central torso, fading on pressure) may transiently occur.
- *3rd week*: ↑ toxicity with persistent high temperature, delirium; weak with feeble pulse, tachypnoea +/− basal crepitations, profuse 'pea soup' diarrhoea. Look and listen for abdominal distension and absent bowel sounds. Neurological complications may occur (may rarely be the presenting complaint).
- *4th week*: if patient survives, fever, mental state, and abdominal distension gradually improve.
- Intestinal haemorrhage, perforation, and peritonitis may occur at any time, most commonly in weeks 2–4. If death occurs it is usually during weeks 2, 3, or 4.

Diagnosis

Culture of bone marrow (~75% culture +ve) or blood (~50% culture +ve; concentration of bacteria in bone marrow ~10× greater than in blood). Positive stool/rectal swab cultures may indicate either acute infection, or carriage with the acute illness having another cause. The Widal and other serological tests have poor sensitivity and specificity (giving many false +ve and false –ve results) and are not recommended for diagnosis.

Management

Early antibiotic treatment essential to prevent complications and death. Start treatment empirically if clinical suspicion strong—see Box 17.11.

- *Consider dexamethasone*: 3mg/kg IV stat, then 1mg/kg qds for 2d for patients with shock or ↓ consciousness. May ↓ mortality.
- Observe toxic patients carefully for signs of GI haemorrhage (manage conservatively with blood transfusion if required for significant blood loss) or peritonitis (treat with surgery).

Relapse

5–10% of treated patients relapse after initial treatment, even if the organism is susceptible to the antimicrobials used. Relapses tend to occur within 1mth of end of treatment; are generally milder and shorter than 1° illness, but may be equally severe. Second and third relapses have been reported. Arrange follow-up if possible. Co-infection with schistosomes may result in chronic or recurrent fever, since bacteria survive within adult worms, protected from antimicrobials.

Prevention

Good sanitation, clean water, and safe food are the most important preventative measures. Standard infection control precautions are indicated in the management of cases to prevent transmission.

Three vaccines are currently available (➲ Immunization, p. 858):

- Live attenuated oral vaccine (Ty21a) requires three doses over 5d with a booster every 5yrs. Not recommended for children <6yrs.
- Unconjugated Vi polysaccharide vaccine, given as a single dose IM; boosters every 3yrs. Not recommended for children <2yrs.
- Conjugated Vi polysaccharide vaccine, given as a single IM dose from age ≥6mths. Recommended for routine use in typhoid endemic countries and in high-risk groups.

Vaccines for paratyphoid are in development.

Box 17.11 Treatment of typhoid

In most areas of the Americas, first- and second-line antimicrobials can be used. In many areas of Asia and Africa, infection with MDR strains (resistant to the first-line antimicrobials chloramphenicol, amoxicillin, trimethoprim–sulfamethoxazole) is common. Reduced susceptibility to fluoroquinolones (nalidixic acid resistance) and full resistance to fluoroquinolones also occur, particularly in Asia, as well as XDR strains with resistance to extended-spectrum cephalosporins.

First-line antimicrobials

- Chloramphenicol 1g oral qds for 14–21d.
- Amoxicillin 500mg oral tds for 14d.
- Trimethoprim–sulfamethoxazole 960mg oral bd for 14d.

Nalidixic acid susceptible MDR strains

- Ciprofloxacin 500–750mg oral bd for 7–10d.
- Ofloxacin 400mg oral bd for 7–10d.
- Ceftriaxone 50–80mg/kg IV od for 10–14d.
- Azithromycin 500mg oral od for 7d (not in severe disease).

Nalidixic acid/fluoroquinolone-resistant MDR strains

- Ceftriaxone 50–80mg/kg IV od for 10–14d.
- Azithromycin 500mg oral od for 7d (not in severe disease).

XDR strains resistant to extended-spectrum cephalosporins

- Azithromycin 500mg oral od for 7d (not in severe disease).
- Meropenem 1g IV every 8h for 10–14d.

In severe disease

- Consider adding dexamethasone 3mg/kg IV stat, then 1mg/kg qds for 2d.
- Antibiotics doses may be ↑ 1.5× initially and given IV.

Public health note

- Typhoid fever vaccination may be offered to travellers (including those visiting friends and relatives) to destinations where risk of typhoid fever is high, especially if staying in endemic areas >1mth or visiting locations where antimicrobial resistant *S. enterica* serovar Typhi common.
- Routine immunization from age ≥6mths is recommended by WHO in typhoid endemic areas and high-risk populations.

Rickettsioses

Rickettsioses are zoonoses caused by small intracellular Gram –ve bacilli. Ticks, fleas, or mites act as vectors and/or reservoirs; the commonest is African tick bite fever.

Spotted fever group

Usually transmitted by the bite of ixodid (hard) ticks. Dogs, rodents, and other animals are reservoirs. After 3–14d (usually 5–7d) of incubation, fever, headache, muscle pain, rash, local lymphadenopathy, and an inoculation eschar (small ulcer with black centre and red areola; see Colour Plate 22c) typically develop.

- *Rocky Mountain spotted fever* (*Rickettsia rickettsii*, USA): often severe, mortality 13–25% in untreated cases. There is no eschar.
- *Boutonneuse fever or Mediterranean spotted fever* (*R. conorii*, Africa, India, Europe, and the Middle East): usually less severe, but occasional fatal cases occur, esp. in elderly or when treatment has been delayed.
- *Rickettsialpox* (*R. akari*, eastern USA and former Soviet Union): transmitted by mites. Rash vesicular—may be confused with chickenpox.
- *African tick bite fever* (*R. africae*, sub-Saharan Africa: most common. More fully described in African tick bite fever, p. 696; Table 17.6.
- *Flea-borne spotted fever/cat flea typhus* (*R. felis*, worldwide): recently recognized illness with clinical picture similar to spotted fever group. Transmitted by cat flea.
- *Other types*: Queensland tick typhus, and North Asian tick fever.

Typhus group

Epidemic (louse-borne) typhus fever (Rickettsia prowazekii)

R. prowazekii is transmitted between humans by the human body louse in cold, unhygienic conditions, particularly during war and famine (Fig. 17.2). The disease is endemic in mountainous areas in eastern Africa, Mexico, Central and S America, and Asia.

- Rickettsiae are excreted in faeces of infected lice and inoculated into abrasions or bite wound by scratching.
- After 1–2wks' incubation, abrupt onset of fever, headache, prostration, myalgia, conjunctival injection, rales. No eschar. Macular rash appears on days 5–6. Fatality ranges from 10% to 40% (untreated) and with age.
- Brill–Zinsser disease is a milder recrudescent disease, which may occur years later in those who have not been adequately treated.
- In the eastern USA, flying squirrels have been the source of occasional human infections that tend to be milder than classical typhus.

Endemic (flea-borne) typhus fever (Rickettsia typhi)

Transmitted from rats → humans by fleas. Found worldwide, esp. in warm, humid climates, where rats and humans coexist. Rickettsiae transmitted via flea faeces by scratching itchy flea bites. Illness similar to louse-borne typhus, but milder.

Scrub typhus

Scrub typhus *(Orientia tsutsugamushi*) transmitted by the bite of trombiculid mites living in sharply delimited rural and suburban areas ('mite islands') in Central, E, and SE Asia, and northern Australia.

- Punched-out eschar develops in ~50% after 6–21d followed by severe acute febrile illness resembling typhus. Deafness and pneumonitis are common. Case fatality varies with infecting strain and ↑ age.
- Unlike other rickettsial illnesses, repeat infections may occur, since immunity does not cross-protect against heterologous strains.

Diagnosis and management of rickettsial infection

Diagnosis

Often clinical in suitable epidemiological setting, if typical triad of fever, rash, and eschar are present (see Colour Plate 22c). Can be verified by serology—but typically only positive ~1–10d after onset of clinical illness. (preferably immunofluorescence; classical Weil–Felix test is obsolete); PCR on blood, swab from eschar or skin biopsy, or isolation of rickettsiae in cell culture from such samples early in infection, are possible, but not widely available.

Management

Give antibiotics (in severe cases, drugs can be given IV):

- Doxycycline 100mg oral bd or 200mg od for 10–14d. Duration varies for different diseases. In some situations (e.g. louse-borne typhus), a single 200mg dose is sufficient.
- Alternative: chloramphenicol 500mg oral qds for 7–10d.
- Quinolones, like macrolides, are effective but are not optimal for moderate or severe spotted fever infections. IV quinolones are useful in severe cases when oral doxycycline cannot be used or when the diagnosis is not confirmed. They are not effective in scrub typhus.

Paediatric note

Doxycycline is favoured for treatment of moderate to severe rickettsial infections in children and pregnant women. Milder infections in children and pregnant women can be treated with azithromycin 10mg/kg/d for 3d.

Severe infections often benefit from a few doses of doxycycline before changing to azithromycin.

African tick bite fever

Epidemiology

- Seroprevalence is ≥70% among adults living in endemic areas in southern Africa. Whereas reports on African tick bite fever in indigenous populations are scarce, a large number of cases are reported in travellers from Europe and elsewhere.
- Vectors are ixodid *Amblyomma* ticks, mainly *A. variegatum* (the tropical bont tick) and *A. hebraeum* (southern African bont tick; Fig. 17.3). Infection in ticks is maintained at very high levels (30% to >70%) by trans-ovarial transmission (from adult female → offspring) and trans-stadial transmission (from larva → nymph → adult). Ticks are aggressive

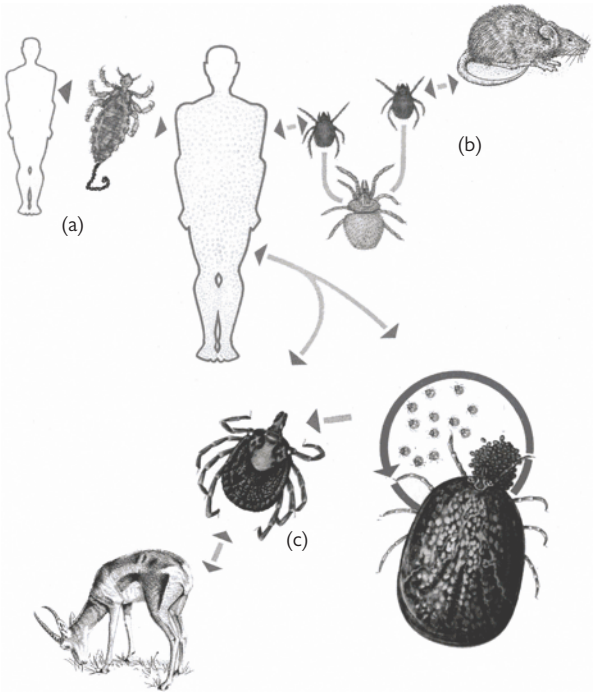

Fig. 17.2 Life cycles of rickettsial infections. (a) *Epidemic (louse-borne) typhus*. Body louse, *Pediculus humanus* feeds on patient infected with *R. prowazekii*; new host is infected when louse faeces are inoculated into skin. (b) *Scrub typhus*: larvae of trombiculid mites are infected with *Orientia tsutsugamushi* from feeding on infected animal or trans-ovarially; humans accidentally infected when bitten. (c) *African tick bite fever*: infection with *R. africae* is prevalent in many animal species and sustained in *Amblyomma* ticks trans-ovarially and -stadially; humans accidentally infected when bitten. Adapted from G. Piekarski, *Medical parasitology in plates*, 1962, with kind permission of Bayer.

and actively seek mammalian hosts, crawling up the legs before attaching to thin, moist skin esp. in folds behind knees, groin, and buttocks.
- Patient has typically walked in long grass, e.g. in game reserve, within 10d preceding onset. Rainy season is time of greatest tick abundance, but infections may be acquired at any time of year.

Clinical features
- Most patients present with abrupt onset of fever, nausea, fatigue, headache, and myalgia.
- Neck muscle myalgia is prominent, with subjective neck stiffness.

- Inoculation eschar is present in most cases but may be overlooked, particularly on dark skin, in hair, or on the perineum. Sometimes, non-typical eschars mimicking acne are seen (Fig. 17.4).
- Rash is typically a maculopapular erythema, becoming confluent in areas, with regional lymphadenopathy draining the site of eschar. Rash may be absent or there may occasionally be scattered vesicles. Reactive arthritis occasionally occurs.
- Severe illness with multisystem involvement including bleeding is noted in a small percentage of cases especially infections with *R. conorrii*. Differentiation from Crimean–Congo haemorrhagic fever (CCHF) and other severe bacterial and viral infections must be considered.

Diagnosis In first 10d of illness, ↑ CRP and moderate lymphopenia seen in most cases; ↑ liver enzymes in ~40% and ↓ platelets in ~20%. Diagnosis can be confirmed in most cases by +ve rickettsial serology, but usually only after the acute illness. Serology lacks sensitivity and specificity for *R. africae*. PCR of eschar swab often positive.

Treatment Give doxycycline 100mg oral bd for 7d or until 48h without fever; most cases improve in 48h. Azithromycin is an alternative for pregnant women and young children; in severe cases, start with doxycycline for a few doses then change to azithromycin.

Table 17.6 Signs and symptoms in African tick bite fever

Characteristic	Frequency (%)
Fever	59–100
Headache	62–83
Myalgia	63–87
Neck muscle myalgia	81
Inoculation eschar	53–100
Multiple eschars	21–54
Regional lymphadenitis	43–100
Cutaneous rash	15–46
Maculopapular rash	15–26
Vesicular rash	0–21
Aphthous stomatitis	11

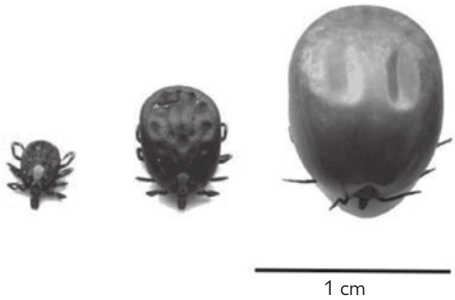

Fig. 17.3 *Amblyomma hebraeum* (vector of African tick bite fever): females at different feeding stages: unfed, partially fed, and fully engorged. Image courtesy Alex Smith, University of Alberta, Canada.

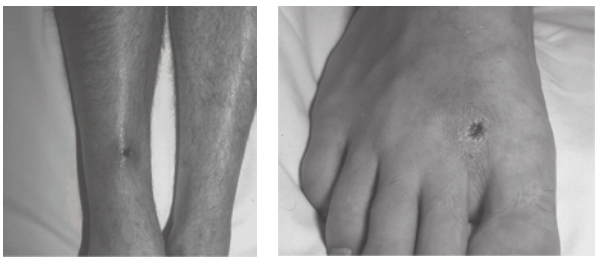

Fig. 17.4 Eschars at the site of vector bites resulting in rickettsial infections. Left: eschar on shin, with surrounding halo of erythema and macular rash in patient with African tick bite fever (*R. africae*). Right: eschar of scrub typhus (*Orientia tsutsugamushi*) without a rash.

Bartonella infections

Bartonellas are intracellular bacteria with tropism for erythrocytes and endothelial cells. Clinical features overlap.

- *Bartonella quintana* is transmitted by the human body louse among the homeless, those living in crowded, unhygienic conditions, and during war. It causes *trench fever*, chronic bacteraemia, and endocarditis in the immunocompetent, and *bacillary angiomatosis* (BA) in the immunocompromised esp. HIV/AIDS.
- *B. henselae* is transmitted among cats by the cat flea and to humans by cat scratch or bite. It causes *cat scratch disease* (uncommonly, bacteraemia and endocarditis in immunocompetent persons) as well as BA and *peliosis hepatis* in the immunocompromised.
- *B. bacilliformis* is unlike other bartonellas in being transmitted by sandflies in the Andes; it causes *Oroya fever* (especially in tourists and transient workers) and *verruga peruana* (especially among natives of the Peruvian Andes). See Box 17.12 for notes.
- Other, unusual species are occasionally associated with *endocarditis* (*B. elizabethae*, *B. vinsonii*) or *cat scratch disease* (*B. clarridgeiae*).

Clinical features

- *Trench fever*: acute-onset fever ('5-day fever'), headache, dizziness, and shin pain. Most cases are self-limiting, but illness in some patients may be prolonged, and relapsing in others. A minority develops chronic infection (attacks of fever, chronic bacteraemia, endocarditis).
- *Cat scratch disease*: usually presents as a tender, self-limiting (2–3mths) regional lymphadenopathy without fever. Complications are rare: retinitis, encephalopathy, visceral forms.
- *Bacillary angiomatosis and peliosis hepatis*: due to vascular proliferative lesions, respectively, in the skin or liver/spleen, but can involve any organ. Typically occur in immunocompromised (HIV+ve) patients. Skin lesions are nodules or papules which may be red to purple, may ulcerate, or bleed (Fig. 17.5).
- *Endocarditis* mainly affects middle-aged patients, presenting with fever, emboli, and occasionally glomerulonephritis. Previously normal or damaged valves may be infected.

Diagnosis

- *Serology*: extensive cross-reactions between *B. henselae* and *B. quintana*.
- PCR of lymph node aspirate, tissue biopsy, or blood.
- Culture from blood is possible, but technically difficult.
- For cat scratch disease and bacillary angiomatosis, organisms can be seen in tissue sections stained with Warthin–Starry silver stain (but not Gram or ZN stains).

Management

- *Trench fever*: doxycycline 200mg po od for 4wks plus gentamicin 3mg/kg IV od for the first 2wks.
- *Cat scratch disease*: no therapy needed, unless extensive or complicated: azithromycin 500mg po on day 1 then 250mg po on days 2–5.
- *Bacillary angiomatosis* and *peliosis hepatis*: azithromycin 250mg po od or erythromycin 500mg po qds for 2–3mths or doxycycline.

Box 17.12 *Bartonella bacilliformis:* Oroya fever and *verruga peruana*

Clinical features

- *Oroya fever*: has a variable incubation period (~2mths) followed by fever and severe anaemia, and in some cases, multiple organ failure. Death is frequently caused by opportunistic bacterial (esp. salmonellosis and *Staphylococcus aureus*), protozoal, or viral infections.
- *Verruga peruana*: may follow Oroya fever or occur independently; the classical presentation is that of recurrent crops of erythematous papules, nodules, or angioma-like skin lesions, caused by vascular endothelial proliferation. The verrucae dry up and slough, leaving no scars. Usually relatively benign, lesions may bleed or become 2° infected.

Diagnosis

- History of travel and possible exposure.
- Serology; PCR of blood, in reference laboratories.
- Examine peripheral blood films for bacilli within or adherent to erythrocytes.

Management

- *Oroya fever*: ciprofloxacin 500mg po bd for 10d.
- *Verruga peruana*: rifampicin or streptomycin may ↓ size and pain of large lesions.

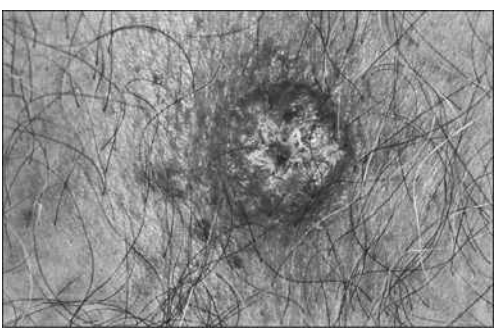

Fig. 17.5 Cutaneous lesion ~1cm diameter of bacillary angiomatosis (*Bartonella henselae*) in a patient with advanced HIV infection.

Ehrlichia infections

Human ehrlichioses are tick-borne zoonoses caused by intracellular bacilli. The organisms are found in vacuoles within leukocytes where they divide to form a cluster (morula). *Ehrlichia chaffeensis* infects monocytes while *E. ewingii* and *Anaplasma phagocytophilum* infect neutrophils.

- *E. chaffeensis* and *E. ewingii* are transmitted to humans by the *Amblyomma americanum* tick from a variety of mammals, esp. deer and dogs; occurs in the southern USA.
- *A. phagocytophilum* is transmitted to humans by *Ixodes* spp. ticks from mammals, esp. ruminants and rodents; occurs in the USA and Europe.

Clinical features

Ehrlichiosis presents with an acute flu-like illness, which may be accompanied by rash, vomiting, and meningoencephalitis. Leukopenia, thrombocytopenia, and ↑ liver enzymes levels are common. Illness caused by *E. chaffeensis* is generally more severe, with ~3% mortality. *E. ewingii* generally causes disease in immunocompromised patients.

Diagnosis

- Serology or PCR, in reference laboratories.
- Examination of Giemsa-stained peripheral blood films for morulae within neutrophils or monocytes.

Management

Doxycycline 100mg bd po or IV for 7–10d.

Paediatric note

Rifampicin can be used for ehrlichiosis in pregnancy or in children; neither erythromycin nor azithromycin are thought to be effective.

Public health note

Control or avoidance of the vectors: delousing of clothing and body with powder; preventive measures against tick bites.

- *Lice*: apply residual insecticide powder (e.g. 1% permethrin, 30–50mg/adult) to clothes and persons in situations favouring infestation; reapply regularly. Provide facilities for bathing and washing clothes and bedclothes. In epidemic situations, apply residual insecticide to all contacts or the entire community.
- *Ticks*: look for and remove attached or crawling ticks after exposures. De-tick dogs and use canine-appropriate acaricides. Use tick repellents and protective clothing to avoid contact.
- *Fleas*: for bubonic plague control, apply residual insecticides to rat burrows or harbourages. Wait until flea populations have been reduced before instituting rodent control measures (to avoid human exposure to fleas).

Cat scratches and bites should be thoroughly cleaned and cat fleas controlled to prevent cat scratch disease.

Coxiella infections

Coxiella burnetii is an intracellular coccobacillus that causes *Q fever*. It infects a wide variety of animals (esp. cattle, sheep, and goats), and ticks. Animals shed *C. burnetii* in milk, faeces, urine, and particularly birth by-products. Hides and wool may be contaminated with tick faeces containing concentrated organisms. Humans acquire infection through inhalation of infected aerosols (which may be air-borne over considerable distances), ingestion of unpasteurized dairy products, or contact with contaminated clothing. Person-to-person spread is rare.

Clinical features

Q fever may be asymptomatic or present as an acute flu-like illness with varying severity of hepatitis and pneumonia. Aseptic meningitis or encephalitis is more common in some areas. Culture –ve endocarditis is an important chronic presentation, usually on a previous damaged or prosthetic valve. *C. burnetii* can recur in pregnancy → abortion. It may also cause a chronic fatigue-like syndrome.

Diagnosis

- *Acute Q fever*: serology on acute and convalescent samples. Phase II antibodies higher than phase I.
- *Chronic Q fever*: phase I antibodies higher than phase II.
- PCR, immunostaining or EM of liver biopsy or heart valve in reference laboratories.

Management

Doxycycline 100mg oral bd for 7–10d. *C. burnetii* endocarditis requires 18mths of doxycycline plus hydroxychloroquine.

Paediatric note

- Co-trimoxazole or azithromycin are used for the treatment of Q fever in children.
- Erythromycin 10–15mg/kg qds for 7–10d may also be used to treat Q fever in children.

Public health note

Persons at risk of Q fever (abattoir workers, farmers, researchers) should be educated on sources of infection and safe disposal of infected materials (esp. birth products). Milk should be pasteurized. Q fever vaccine is available for those at high risk in some countries.

Relapsing fevers

These are acute febrile illnesses caused by *Borrelia* spirochaetes. Untreated infections relapse repeatedly with afebrile intervals of 5–9d. As well as clothes/body lice and ticks (Fig. 17.6) *Borrelia* are, rarely, transmitted by blood transfusion, needle sticks, and transplacentally.

Louse-borne relapsing fever (LBRF)

Transmission

Epidemic louse-borne relapsing fever, caused by *B. recurrentis*, is transmitted by human clothes/body lice (*Pediculus humanus corporis*) (Fig. 17.6). Lice are infected by feeding on human blood. They transmit *B. recurrentis* to a new human host not by bites, but by inoculation of infected louse faeces through broken skin or intact mucosae, by scratching. Humans are sole host and reservoir.

Epidemiology

LBRF is now confined to Northeast Africa. In the cold, rainy season when people wear more clothes and crowd together for warmth, conditions encourage louse infestation and transmission. Historically, LBRF caused massive pandemics in Africa, the Middle East, and Europe (1903–1936, 50 million cases with 5 million deaths; 1943–1946 10 million cases), exacerbated by wars, crowding, floods, famines, and forced migration.

Since 2015, almost 100 cases of LBRF have been identified in young, mainly male, refugees from the Horn of Africa arriving in several European countries.

Clinical features

- Incubation is 4–18d (average 7d).
- Symptoms start with sudden high fever, chills/rigors, headache, confusion, myalgias, arthralgias, fatigue, dizziness, cough, anorexia, nightmares, and prostration.
- Examination reveals bleeding (epistaxes, subconjunctival haemorrhages, petechiae), tender splenomegaly and hepatomegaly, jaundice, and chest signs.
- The first attack ends dramatically with a febrile crisis, either spontaneously on about the 5th day if untreated or with a Jarisch–Herxheimer reaction (Box 17.13) precipitated by antibiotic treatment.
- Inadequately treated patients may suffer their first relapse about 1wk later. Subsequent attacks tend to be less severe.

Complications Pregnant women have high risk of abortion. Death is due to myocarditis, liver failure, severe bleeding due to thrombocytopenia, DIC, and hepatic dysfunction; ruptured spleen, splenic infarctions, and bacterial superinfection (dysentery, salmonellosis, typhoid, typhus, malaria, TB). During the Jarisch–Herxheimer reaction, patients may die from hyperpyrexia, shock, or pulmonary oedema. Untreated case fatalities ~40% occur during epidemics; treatment can reduce this to <5%.

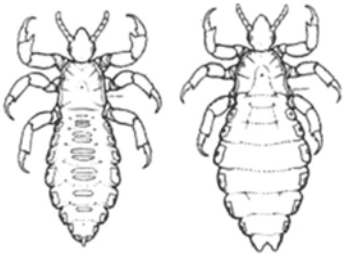

Fig. 17.6 Human body lice (*Pediculus humanus corporis*), the vector of LBRF and epidemic typhus. Adult lice are 2.3–3.6mm long. Body lice live and lay eggs on clothing and move to the skin to feed. Lice spread by close contact, esp. with crowding/poor hygiene. Animals do not play a role in the transmission of human lice.
Source: Drawing by J H Grundy, courtesy of D A Warrell.

Box 17.13 Jarisch–Herxheimer reactions in spirochaete infections

Acute inflammatory exacerbation of symptoms and pathology following treatment is most frequent (33–100%) and severe in LBRF, although it also occurs in TBRF, Lyme disease, leptospirosis, syphilis, and other spirochaetal infections.

Within a few hours of treatment, patient becomes restless, then develops violent rigors with soaring temperature, respiratory, and pulse rates, high BP, and associated vomiting, diarrhoea, coughing, and delirium.

This is followed by the flush phase during which there is profuse sweating and vasodilatation, sometimes complicated by hypovolaemic shock or acute pulmonary oedema from myocarditis.

Treatment

For severe Jarisch–Herxheimer reactions precipitated by antibiotics:

- Control pyrexia by physical cooling.
- Prevent hypovolaemia with IV fluids.
- Nurse in bed for 48–72h to prevent fatal postural hypotension.

Treat acute pulmonary oedema and myocarditis with IV digoxin. No effective antibiotic regimen has yet been shown to cause fewer Jarisch–Herxheimer reactions, but in highly vulnerable patients, initiate treatment with IM procaine penicillin and give doxycycline the next day.

Tick-borne relapsing fever (TBRF)

Endemic TBRF is caused by >15 *Borrelia* spp. and transmitted by soft ticks (*Ornithodoros*), and in the case of *B. miyamotoi*, by hard ticks (*Ixodes*) (Fig. 17.7). TBRF is widely distributed in tropical and temperate countries esp. Africa, but not Australasia and Pacific islands.

Transmission

Ticks are infected by feeding on animal or human blood or acquire spirochaetes congenitally (trans-ovarially). They transmit *Borrelia* to animals or humans during a blood meal. They are reservoirs as well as vectors. Peridomestic rodents are the main vertebrate reservoir. Ecology and species of *Borrelia* and tick vary geographically. Only classic E African TBRF (*B. duttonii*) is anthroponotic (not a zoonosis). Risk of infection is associated with sleeping in tick- and rodent-friendly huts. Tick bites are painless. They feed for only a few hours at night and then drop off, so exposure is usually unsuspected.

Clinical features

After incubation of 2–18d, symptoms resemble LBRF, usually milder and briefer, although ARDS and severe Jarisch–Herxheimer reactions have been reported.

- Fever, epistaxis, abdominal pain, diarrhoea, and cough.
- Splenomegaly and splenic infarction are common; hepatomegaly and jaundice are unusual.
- Transient neurological problems in 5–10%: paraesthesiae, cranial nerve palsies (esp. VII), visual symptoms, hemiparesis or paraparesis, lymphocytic meningitis.
- Erythematous and petechial rashes may appear.
- Fever may recur up to 13 times, separated by a few days–3wks in untreated patients.
- Miscarriage in up to 1/3 of pregnant cases.

Diagnosis of the relapsing fevers

LBRF is easily diagnosed by finding spirochaetes (sometimes in vast numbers, e.g. >500,000/mm^3) in Giemsa-stained blood films (Fig. 17.8 and ➲ Colour plate 24). However, in TBRF, spirochaetaemia may be scanty and intermittent, making microscopy insensitive. PCR of blood is accurate; serology is unhelpful.

Management of tick- and louse-borne relapsing fever

Single-dose antibiotic therapy is curative for LBRF:

- Adults: doxycycline 100mg or tetracycline 500mg, oral (for sick patients, tetracycline 250mg IV) stat.
- Pregnant women or children: erythromycin adult 500mg, children 10mg/kg oral (for sick patients, erythromycin IV) stat *or*
- For mixed infections with louse-borne typhus (adults): doxycycline 100–200mg oral stat.
- Benzylpenicillin and chloramphenicol are also effective.

For TBRF, 10d courses of the same drugs are required. For treatment of Jarisch–Herxheimer reactions, see Box 17.13.

Public health note: control of relapsing fever

- *LBRF*: washing clothes in hot water (>60°C) for >10min kills clothes lice and their eggs. Isolating infested clothing away from wearers for 7–10d starves lice to death. Insecticides are also effective. Patients should be bathed with soap. Head lice should be removed by washing or shaving, although their role in LBRF is unproven. These measures are essential to control an epidemic.
- *TBRF*: kill or deter ticks with residual insecticides in dwellings, repellents (DEET), improved house construction, rodent control.

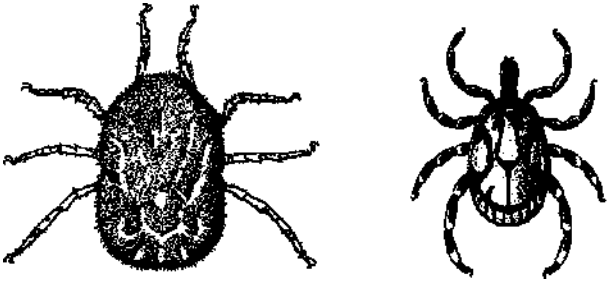

Fig. 17.7 Left: soft tick (genus *Ornithodoros*) vector of tick-borne relapsing fever. Right: hard tick (genus *Ixodes*) vector of *B. miyamotoi*, Lyme disease, rickettsial infections, and tick-borne encephalitis.

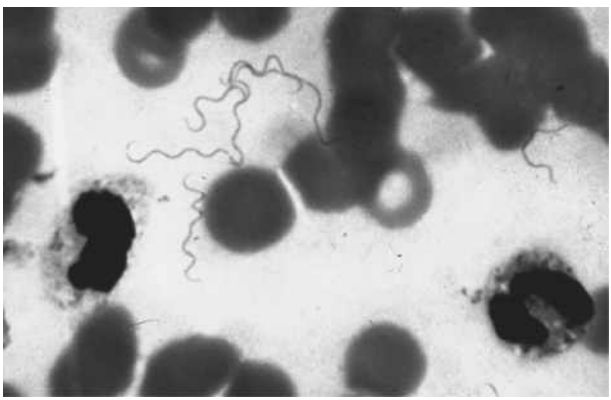

Fig. 17.8 Blood film showing several *B. duttonii* spirochaetes in a patient with untreated TBRF.

Leptospirosis

A zoonosis caused by *Leptospira* spirochaetes. Leptospires are excreted in urine of wild and domestic animals into water sources and can survive for days in warm, damp conditions esp. fresh water and damp soil. Exposure can → self-limiting or serious, sometimes fatal, disease.

Epidemiology and transmission

- Global distribution, esp. tropics (incidence ≥10/100,000 population; seroprevalence ~5–10%).
- *Leptospira* spp. can be divided into 25 serogroups and >250 serovars; or by genotyping into >17 genomospecies. Not all are pathogenic.
- The commonest source of infection is rats; wild and domestic animals (e.g. cattle, pigs, dogs) are also reservoirs of infection and can excrete large numbers of leptospires in urine for long periods.
- Leptospires enter the body through cuts or abrasions of skin or mucous membranes after immersion in contaminated water (pools, canals, rivers), or through close animal contact.
- Risk groups are those in contact with contaminated water or infected animals during occupational or recreational activities, e.g. farmers, sewage or abattoir workers, military personnel, humanitarian workers, adventure travellers (trekking or water-based activities). Epidemics may occur after heavy rains or flooding.
- Human-to-human transmission, incl. congenital infection is rare.

Clinical features

Following infection, leptospiraemia spreads spirochaetes to multiple organs. Incubation period is ~10d (range 5–14d). Disease severity correlates with leptospire burden. Leptospirosis pathogenesis remains poorly understood but involves small vessel endothelial cell injury. Clinical manifestations reflect organ dysfunction resulting from direct effects of leptospires and/or host immune responses to infection. There are three clinical categories:

- *Subclinical infection*: common in endemic areas.
- *Self-limiting infection*: infection is followed 1–2wks later by sudden-onset fever, headache, severe myalgia (characteristically affecting calves and lower back), N&V, and conjunctival suffusion or haemorrhage. Cough is common.
- *Severe disease*: multisystem illness with high fever, jaundice, renal failure, and respiratory failure, which may be complicated by pulmonary haemorrhage and haemoptysis (Weil's disease). Illness may be biphasic with ~2d remission after the first 4–7d, followed by a second immunopathological phase when the patient's condition worsens with persistent high fever, meningoencephalitis, myocarditis, widespread haemorrhage, renal failure, jaundice, and shock.

Case fatality ranges from ~2% in uncomplicated disease to ≥19% in jaundiced patients, and ↑ with advancing age. Maternal infection may → fetal loss.

Diagnosis

The differential diagnosis of uncomplicated disease is wide (e.g. malaria, dengue, rickettsial infection, community-acquired pneumonia). Bloods may show ↑ WBC (neutrophilia) +/− ↓ platelets, ↑ CK. Renal and hepatic impairment are common, typically with ↑ bilirubin but only modestly ↑ ALT/AST. Urine frequently contains blood, protein, and WBCs. CSF findings are those of aseptic meningitis.

Culture Slow-growing leptospires can be isolated from blood or CSF (days 7–10d of illness) or urine (weeks 2–3). However, culture is not sensitive and too slow to make the diagnosis during the acute phase.

Serology Antibodies are usually detectable from day 5–7 of the illness, although seroconversion may be delayed. The microscopic agglutination test (MAT) performed on paired sera is the standard diagnostic test. Rapid tests are available but generally of low sensitivity.

PCR Quantitative PCR on serum or urine, if available, is reliable early in the course of the illness.

Management

Antibiotic therapy provides greatest benefit early in the illness.

Supportive treatment includes cardiovascular support for sepsis; early renal replacement therapy; and ventilatory support if indicated.

- *Mild disease*: doxycycline 100mg bd for 7d, started <3d after onset of symptoms, will hasten recovery. Alternatives are azithromycin 1g, followed by 500mg at 24h and 48h; or amoxicillin 25–50mg/kg/d in three divided doses for 7d.
- *Moderate or severe disease*: benzylpenicillin 1.2–2.4g IV qds for 5–7d (even if patient has been ill for several days). Alternatives for severe disease: ampicillin 1g IV qds or cefotaxime 1–2g IV every 12h or ceftriaxone 1–2g IV od.

Complications

The Jarisch–Herxheimer reaction may occur after starting antibiotics in some patients (➲ p. 705).

Public health note: control of leptospirosis

- ↓ *exposure*: education of high-risk groups, personal protective equipment (PPE).
- ↓ *animal transmission*: control of rodent populations and vaccination of domestic animals.
- *Prophylaxis*: doxycycline 200mg weekly has been shown to ↓ clinical disease (but not infection) in populations with very high risk of exposure over a limited time.

Immunization: commercial vaccines with limited protective efficacy against certain serotypes have been produced for use in humans but are not widely available.

Brucellosis

A zoonosis of worldwide distribution caused by the Gram –ve bacillus, *Brucella*. There are ~500,000 human cases/yr. Responsible species are: *Brucella melitensis* (sheep, goats, camels), *B. abortus* (cattle, buffalo, yaks, camels), *B. suis* (pigs, hares, rodents, caribou, reindeer), *B. ovis* (sheep), and *B. canis* (dogs). *B. melitensis* is the commonest. The organism lives and multiplies within phagocytes in the reticuloendothelial system. The cellular immune response, in particular the interferon-gamma pathway, is important in pathogenesis.

Transmission

Infected animals shed large numbers of bacilli in milk, urine, and products of conception. Humans infected either by:

- Sporadic cases occur by direct contact with infected animals (entry is through breaks in skin or inhalation of aerosols in stables, abattoirs, and laboratories).
- Sporadic cases and outbreaks occur by ingestion of unpasteurized milk, soft cheese (Fig. 17.9), yoghurt, butter, and ice-cream.

Clinical features

Variable incubation period (usually 2–4wks, may be months), followed by acute or insidious onset of fever (may be rigors), and non-specific constitutional symptoms (sweating, anorexia, malaise, headache, back pain). Lymphadenopathy and hepatosplenomegaly may be present. Complications can affect virtually any organ system, including:

- Osteoarticular (spondylitis, peripheral arthritis, sacroiliitis).
- Reproductive (epididymo-orchitis, spontaneous abortion).
- Hepatitis, peritonitis.
- CNS (meningitis, encephalitis, abscess).
- Endocarditis (responsible for most mortality).

Diagnosis

The serum agglutination test is most widely used (single titre >1:160 or rising titre), but cross-reacts with other Gram –ves. ELISA (IgG, IgM, IgA) has ↑ sensitivity and specificity. Rapid (dipstick-type) serological tests are commercially available. PCR is promising. Culture from blood or tissue is confirmatory, but is relatively insensitive and requires prolonged incubation. When cultured, it is readily transmitted to laboratory staff via aerosols produced by laboratory procedures.

Management

Optimal treatment 6wks of doxycycline 100mg oral bd plus 6wks of rifampicin 300mg oral bd plus an aminoglycoside for first 2–3wks: either streptomycin 15mg/kg IM daily or gentamicin 5mg/kg IM od.

Alternative Doxycycline plus rifampicin (as above-described) for 6wks, but relapse rate higher in regimens that do not include an aminoglycoside. Ciprofloxacin/ofloxacin may be added as an alternative third agent. Rifampicin plus co-trimoxazole are useful in pregnancy. HIV+ve individuals respond to the same regimens used for HIV–ve individuals.

Paediatric note: paediatric doses

Children aged >9yrs may be treated as adults. For younger children, combine two of the following:

- Rifampicin 15mg/kg (max. 600mg) oral od for 6wks.
- Co-trimoxazole: sulfamethoxazole 20mg/kg + trimethoprim 4mg/kg (max. 800 + 160mg) oral bd for 6wks.
- Gentamicin 2.5mg/kg IV or IM tds for first 2wks.

Public health note: prevention and control

- Pasteurize (or boil) milk products.
- PPE (masks, gloves, etc.) for those at occupational risk, e.g. vets.
- Screen livestock by serology or by testing cow's milk and eliminate infected animals.
- Vaccinate animals in high-prevalence areas using live attenuated vaccine (no human vaccine is available; vaccine strains may cause disease in humans if accidentally inoculated and post-exposure prophylaxis with doxycycline for 3wks should be given).
- Identify source of outbreaks (usually milk or milk products from infected herd); recall all affected products.
- Laboratory exposures: give prophylactic rifampicin + doxycycline (or doxycycline alone) for 3–6wks.

Fig. 17.9 Unpasteurized goat cheese, Canta valley, Peru. Unpasteurized cheese may transmit brucellosis.

Source: Image courtesy of D A Warrell.

Plague

An acute febrile illness caused by the Gram –ve coccobacillus *Yersinia pestis*, plague can be rapidly fatal unless treatment is started promptly. Early empiric antibiotic therapy is therefore essential when clinical suspicion is high.

Plague has had a profound effect on the course of human history, mainly through the impact of three pandemics. Although another pandemic is unlikely, plague remains a threat due to high case fatality rates and the potential for epidemic spread (Fig. 17.10).

The plague bacterium cycles among rodents and their fleas in focal areas of Africa, Asia, and the Americas (incl. the western USA). Since 2010, >95% of cases reported to the WHO have been from Madagascar, the Democratic Republic of Congo (DRC), Uganda, and Tanzania. Humans are incidental hosts and can be infected in a variety of ways.

Fig. 17.10 Cases of plague by country, 2013 - 2018. CDC, Atlanta, GA, USA.

Transmission

Bubonic and 1° septicaemic plague occur following the bite of infected fleas or through direct contact with infectious tissues. Peri-domestic rodents (e.g. *Rattus rattus*, *R. norvegicus*) amplify and bring the infection closer to humans during an epizootic. Although many flea species can transmit the bacterium, *Xenopsylla cheopis* is the important vector. Pneumonic plague is the only clinical form that can be directly transmitted from person to person: transmission occurs through respiratory droplets rather than aerosols, typically when the source patient is very ill.

Clinical features

Bubonic plague

The commonest clinical presentation. The first specific sign is local lymphadenitis in the nodes draining the site of inoculation (e.g. flea bite). After 2–7d (always <15d), a 'bubo' forms in these nodes. There is typically a

short prodrome of fever, malaise, headache, and, in some cases, a dull ache in the affected nodes for up to 24h before the bubo appears. The enlarged nodes are extremely painful and swollen, and the mass is non-fluctuant and immobile. The overlying skin may be warm, red, oedematous, and adherent (Fig. 17.11). Mortality is ~50% without treatment.

Pneumonic plague

Pneumonic plague occurs following haematogenous spread of *Y. pestis* to the lungs; either as a complication of untreated bubonic or septicaemic plague, or after direct inhalation of bacteria in droplets coughed from a patient or animal with pneumonic plague.

Intense headache, malaise, fever, and vomiting → rapidly evolving dyspnoea, chest pain, cough, haemoptysis, and prostration. There are often scanty chest signs despite multifocal consolidation or bronchopneumonia on CXR. Respiratory involvement needs to be distinguished from ARDS, which may occur in bubonic and septicaemic plague. Rapid deterioration and death from fulminant pneumonia, sepsis, and multiorgan/respiratory failure is common even with treatment, and without treatment pneumonic plague is usually fatal.

Septicaemic plague

Yersinia sepsis may occur as 1° septicaemia, or as a complication of untreated bubonic or pneumonic plague. GI symptoms (vomiting, diarrhoea, abdominal pain) and skin purpura may be prominent, and it may rapidly → multiorgan failure and death.

Other presentations

Rarer clinical presentations include meningitis, pharyngitis, and cutaneous infections.

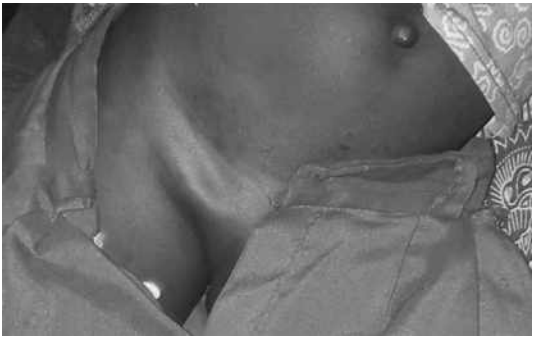

Fig. 17.11 Enlarged inguinal lymph node (bubo) in child with bubonic plague. CDC, Atlanta, GA, USA.

Diagnosis

Consider as a cause of acute febrile illness in a person recently in a plague endemic area. Diagnosis confirmed by aspiration of a bubo for smear (bipolar coccobacilli on Giemsa or Gram stain) and culture; blood for smear and culture; and acute and convalescent serology. If available, antigen detection directly on primary clinical samples (i.e. bubo aspirate) may → rapid diagnosis.

Management

Recommendations are given in Table 17.7. Start empiric IV therapy immediately plague is suspected. Once the patient improves consider IV to oral switch, to complete a 10–14d course. Most experience is with streptomycin. Some regimens shown might be avoided in children and pregnant women in other circumstances, but the life-threatening nature of plague justifies their use.

Table 17.7 Recommended antibiotic treatment regimens

Antibiotic	Adults	Children
Streptomycin	1g IM bd	15mg/kg IM bd (max. 2g/d)
Gentamicin	5mg/kg IV/IM od (max. 500mg)	2.5mg/kg IV/IM tds
Ciprofloxacin	400mg IV bd or tds or 500–750mg po bd	15mg/kg (max. 400mg) IV bd or 20mg/kg (max. 500mg) po bd
Levofloxacin	500mg IV/po od (750mg may be used if clinically indicated)	8mg/kg (max. 250mg) IV/po od
Doxycycline	100mg IV/po bd	2.2mg/kg (max. 100mg) IV/po bd
Chloramphenicol	25mg/kg (max. 750mg) IV/oral qds	25mg/kg (max. 750mg) IV/oral qds

Public health note: prevention and control of plague

- Rodent control measures (e.g. remove rodent food and habitats from vicinity of households).
- Flea control (must occur before rodent control during outbreaks).
- Notify local health authorities of all suspected cases.
- Conduct case finding in affected and nearby households.
- Isolate pneumonic plague patients; use respiratory droplet precautions until ≥48h after starting antibiotics and clinically improving.
- Consider prophylaxis for close contacts of pneumonic plague (e.g. 1° caregivers, medical staff, those within 2–3m of patient); use doxycycline 100mg bd or ciprofloxacin 500mg bd for 7d.
- Vaccination currently not generally available.

Melioidosis

A disease caused by Gram –ve bacteria *Burkholderia pseudomallei* that is endemic in S and SE Asia, northern Australia, the Caribbean, and increasingly reported from elsewhere including areas of Africa and S America. It is a major cause of septicaemia in NE Thailand. The bacteria are present in mud and surface water (e.g. rice paddies), and infection occurs following inoculation, inhalation or ingestion. The time from exposure to illness ranges from 1d to >60yrs, but most cases are acute infection from recently acquired bacteria. Overall case fatality is 43% in NE Thailand (20–30% in children) and 14% in Australia, with ~89,000 deaths per year worldwide from melioidosis. *Glanders* is a similar disease of horses caused by *Burkholderia mallei*, with very rare cases in humans. Diagnose and treat as for melioidosis.

Clinical features

These are very variable, and range from fulminant sepsis and rapid death to a chronic illness characterized by fever, weight loss, and wasting. The most frequent clinical picture is a septicaemic illness, often with bacterial dissemination → pneumonia (50%) and/or abscess formation, most commonly in the liver and spleen (30%) . Infection may occur in bone, joints, skin, soft tissue, parotid gland, testis, prostate, and CNS (Fig. 17.12). Severe sepsis and its complications are the usual cause of death if it occurs.

Diagnosis

- Consider melioidosis in febrile patients with a history of one or more of:
  - Residency in an endemic region or relevant travel history.
  - Any contact with soil or water containing *B. pseudomallei*.
  - Risk factors for melioidosis, e.g. diabetes mellitus or renal disease.
- Diagnostic confirmation relies on culture. *B. pseudomallei* colonization is extremely rare and isolation of even a single colony from any clinical sample can be diagnostic.
- Culture blood, urine, throat swab, and respiratory secretions from suspected patients, together with pus and wound swabs where relevant. Site of culture positivity may not necessarily relate to clinical features (e.g. urine may be +ve without features of UTI).
- *B. pseudomallei* is a hazard group 3 biological agent and requires safe handling during culture, so tell your diagnostic laboratory if you suspect melioidosis.
- *B. pseudomallei* grows on most routine culture media, but as an oxidase +ve Gram –ve rod may be disregarded as an environmental pseudomonad, so be alert to the diagnosis in the right clinical and epidemiological setting. *B. cepacia* agar is often available in Western laboratories (it is used to culture sputum from cystic fibrosis patients) and is a good selective agar for *B. pseudomallei.*
- *B. pseudomallei* can be identified using biochemical tests and susceptibility pattern (resistant to gentamicin and colistin, susceptible to amoxicillin–clavulanate), commercial kits, or automated systems.
- Consider sero-diagnosis in cases of suspected melioidosis who are culture –ve, but interpret with caution. It is common for the healthy population living in regions where infection is endemic to be seropositive, and serology may be falsely –ve in definite cases.

Management

- Start appropriate antibiotics as soon as possible—immediately after culture, or even before culture if sampling is going to be delayed.
- Treatment is divided into IV and oral phases and is required for at least 12wks. Recommendations are given in Box 17.14.
- Use imaging (where available) to detect abscesses in the liver, spleen, and elsewhere. Drain collections of pus wherever feasible.
- Fever clearance is often slow (median 9d), and is not an indication for a change of antimicrobials unless associated with clinical deterioration.
- If blood culture is +ve at presentation then repeat again at 1wk; if still +ve, this is a poor prognostic sign. Review antimicrobial therapy and re-image for pus collections.
- There is no clinical benefit in repeating cultures from other sites. Sputum and draining abscess cultures can be culture +ve for several weeks, but this is not associated with ↑ mortality in a patient who is otherwise responding to treatment.
- Infection is not thought to be easily transmitted from person to person, but infection control measures may be recommended.
- Recurrent melioidosis is common (6% in 1st year and 13% by 10yrs) and is usually due to relapse following failure to eradicate the infecting organism.

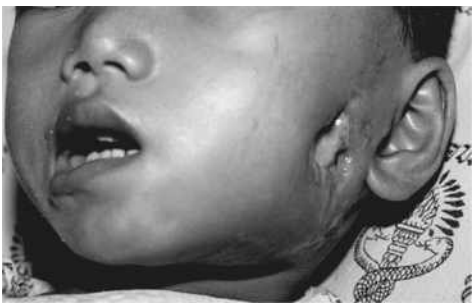

Fig. 17.12 Thai child with melioidosis leading to a parotid abscess, which is discharging pus, and a left VIIth nerve lesion.

Source: Image courtesy of S Looareesuwan and D A Warrell.

Box 17.14 Antimicrobial therapy for melioidosis

Initial parenteral therapy

Give IV therapy for at least 10d and extend to 4–8wks for deep-seated infection incl. complicated pneumonia, deep-seated infection incl. prostatic abscesses, neurological melioidosis, osteomyelitis and septic arthritis.

- *First line*: ceftazidime 50mg/kg per dose (up to 2g) every 6–8h, or meropenem 25mg/kg per dose (up to 1g) every 8h.
- *Second line*: amoxicillin/clavulanate 20/5mg/kg every 4h; this gives equivalent mortality to first-line drugs, but more treatment failure.

Oral eradication therapy Duration of oral therapy, a minimum of 3mths after the end of parenteral therapy.

Adults

Trimethoprim/sulfamethoxazole using a weight-based dosing schedule:

- If <40kg give 2 × 480mg tablets bd.
- If 40–60kg give 3 × 480mg tablets bd.
- If >60kg give 4 × 480mg tablets bd.

Children <8yrs and pregnant women

Children: amoxicillin/clavulanate 20/5mg/kg oral tds.

- For adults <60kg, amoxicillin/clavulanate 1000/250mg oral tds.
- For adults >60kg, amoxicillin/clavulanate 1500/375mg oral tds.

Anthrax

Anthrax is a zoonosis from infection with the spores of the Gram +ve rod *Bacillus anthracis*. Anthrax is a disease of grazing animals (sheep, cattle, goats) in parts of Asia, Africa, S and Central America, southern Europe, Caribbean, and Middle East. The hardy spores remain viable in soil or on animal products for many years.

Transmission

Anthrax is primarily an occupational disease of workers who process hides, hair, bone products, and wool and those who handle infected animals (veterinarians, wildlife workers). Spores may be dispersed by wind, water, scavengers, or transport of animal products. Outbreaks can follow ingestion of contaminated meat. Anthrax spores are resistant and can be aerosolized, so they have been used as agents of bioterrorism.

Clinical presentation

Cutaneous anthrax

Accounts for 95% of naturally occurring cases. Spores are inoculated into the skin through abrasions or cuts. A short incubation period (typically 1–5d) → an itchy papule → a vesicle, ulcer, and finally → a painless black eschar (Fig. 17.13) with extensive local oedema and surrounding purple vesicles. This heals spontaneously in 1–3wks; however, bacteraemic spread and overwhelming septicaemia may occur. Neck lesions may → airway obstruction (consider early tracheostomy).

Inhalational anthrax

Usually occurs 1–4d following exposure, but may be delayed for up to 43d. A biphasic illness, it presents with symptoms of a viral URTI followed by sudden onset of haemorrhagic mediastinitis with fever, hypoxia, dyspnoea, and shock. Treatment in the late stages is usually unsuccessful, with mortality up to 90%.

Gastrointestinal anthrax Follows ingestion of contaminated meat. Severe abdominal pain, bloody diarrhoea, massive ascites, and sepsis occur. Mortality is >50%.

Other forms

Incl. meningitis (which may complicate any of the other forms) and oropharyngeal anthrax. A newly recognized form is injection anthrax, associated with skin-popping (injection into subcutaneous and muscle tissues) of heroin contaminated with spores of *B. anthracis*. An outbreak in Scotland resulted in 47 cases with 13 deaths.

Diagnosis

Rapid diagnosis is by demonstrating Gram +ve bacilli in smears from fluid from under the eschar, or other site-of-disease samples (or using newer methods such as PCR, direct immunofluorescence). Culture blood, LNs, and CSF as appropriate (Box 17.15).

Management

- Early, high-dose antibiotic therapy is vital: give benzylpenicillin 2.4g IV 4hrly for 10d. Naturally (or genetically modified) penicillin-resistant mutants can occur, so until culture and sensitivity available, add ciprofloxacin 400mg IV bd followed by 500mg oral bd. Doxycycline 100mg bd is an alternative.
- Passive immunity: monoclonal antibodies (raxibacumab and obiltoxaximab) have been made available by the Centers for Disease Control and Prevention (CDC), Atlanta, USA, for the treatment of inhalational anthrax, in combination with appropriate antibiotics. They can also be used in prophylaxis, should other treatments be unavailable or inappropriate. Human anthrax immunoglobulin can also be given to provide passive immunity to those exposed to inhalational anthrax. It is used in combination with antibiotics.
- Surgical debridement of the black, necrotic eschar is unnecessary. Eschars become sterile in <2d. However, in injection anthrax prompt widespread debridement of the affected subcutaneous tissue is mandatory.
- *Infection control*: little risk of patient-to-patient transmission; use standard barrier precautions with gloves, gowns/aprons.

Duration of antibiotic therapy

- *Cutaneous*: 7–10d.
- *Inhalational*: at least 14d after symptoms abate.
- *GI*: at least 14d after symptoms abate.

Post-exposure prophylaxis Should be considered following possible deliberate aerosol release—ciprofloxacin 500mg oral bd, or doxycycline 100mg bd, for 60d.

Box 17.15 Differential diagnosis of eschar

Infective causes

- Staphylococcal skin infection.
- Tularaemia.
- Scrub typhus.
- Rickettsial spotted fevers.
- Rat bite fever.
- Ecthyma gangrenosum.

Non-infective causes

- Spider bites.
- Vasculitides.

Paediatric note: paediatric doses for anthrax

- Ciprofloxacin 10–15mg/kg (max. 400mg) IV bd followed by 10–15mg/kg (max. 500mg) oral bd.
- If penicillin susceptible, use IV benzylpenicillin 150mg/kg daily in four divided doses.
- For children >12yrs, use adult doses.

Public health note: prevention of anthrax

- Disinfection: spores are resistant to desiccation, heat, UV light, gamma irradiation, and many disinfectants. For disinfection of discharge from lesions or soiled materials use hypochlorite, hydrogen peroxide, peracetic acid, or glutaraldehyde. Burn or autoclave contaminated material, where possible.
- Vaccination: immunize high-risk persons with cell-free, supernatant-derived vaccine. Regular boosters required.
- Veterinary public health measures: infected carcasses should be incinerated at site, do not bury or transport if possible; immunize all domestic animals at risk, with annual re-immunization.
- Control occupational exposure: control dust; ventilate work areas; wear protective clothing; disinfect wool, hides, and bone prior to processing.

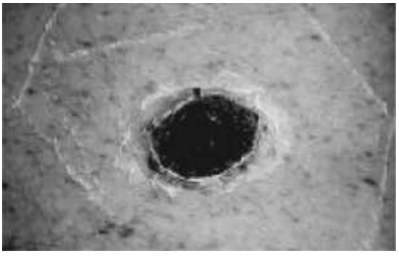

Fig. 17.13 Typical eschar of cutaneous anthrax.

African trypanosomiasis

Human African trypanosomiasis (HAT) or 'sleeping sickness', is a protozoan disease confined to sub-Saharan Africa (Fig. 17.14), caused by *Trypanosoma brucei* spp. Two forms of HAT exist, *T.b. gambiense* and *T.b. rhodesiense*, both transmitted by tsetse flies (genus *Glossina*) (Fig. 17.15), but epidemiological (Table 17.8) and clinical features (Table 17.9) differ.

Epidemiology

Incidence of *T.b. gambiense* HAT has been decreasing since 2000 (2131 cases in 2016). *T.b. rhodesiense* HAT is sporadic (≤100 cases/year), but likely underdiagnosed in some areas. Uganda is the only country with both forms, albeit in different geographical areas.

Table 17.8 Summary epidemiology and transmission of HAT

	T.b. gambiense	*T.b. rhodesiense*
Geography (Fig. 17.14)	Central and W Africa	E and southern Africa (Malawi, Zambia, Zimbabwe, Uganda, Tanzania, Kenya)
Transmission areas	Waterholes, rivers	Savannah, recently cleared bush
Reservoir	Humans	Game animals, cattle
Disease pattern	Endemic	Sporadic (occasional epidemics)

Table 17.9 Summary clinical features of HAT

	T.b. gambiense	*T.b. rhodesiense*
Clinical time course	Chronic, insidious (after asymptomatic phase)	Acute, sometimes fulminant
Inoculation site	Rarely chancre	Often chancre
Symptoms	*Early*: non-specific fevers, pruritus, arthralgia *Late*: CNS symptoms	Fever, malaise, headache, myalgia, arthralgia, cardiac symptoms *Late*: CNS symptoms
Signs	*Early*: LNs *Late*: CNS signs	*Early*: rash, LNs, acute myocarditis, dysrhythmia, heart failure *Late*: DIC, multiorgan failure, CNS signs
Outcomes untreated	Fatal (months–years)	Fatal <1–3mths

Fig. 17.14 Distribution of human African trypanosomiasis. The area southeast of the line = *T.b. rhodesiense* and northwest of the line = *T.b. gambiense*.

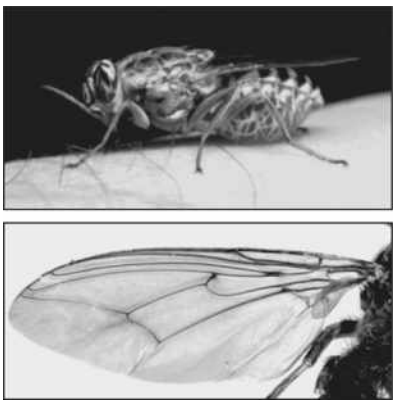

Fig. 17.15 Female tsetse fly (*Glossina morsitans*) engorged with blood after feeding. All *Glossina* flies can be identified by the pattern of 'cells' on their wings. Between the fourth and fifth veins of the wing is the 'hatchet cell'—looks like a butcher's cleaver.

Clinical features

T.b. gambiense HAT is a chronic illness, but *T.b. rhodesiense* HAT is an acute, sometimes fulminant disease. Both forms usually fatal if untreated. An infective tsetse bite → a local inflammatory reaction → an itchy, tender subcutaneous swelling (chancre) (*T.b. rhodesiense*) → regional lymphadenopathy (both types). Invasion of bloodstream and lymphoreticular system follows —the haemolymphatic (early) stage. Trypanosomes then invade CNS, → meningo-encephalitic (late) stage of the disease. Trypanosomes escape host immunological responses by changing surface antigens (antigenic variation; see ➔ Table 17.10, p. 729; see Colour Plate 9a).

Gambian trypanosomiasis

After asymptomatic phase (months–years), the early stage is characterized by irregular fevers, fatigue, arthralgia, myalgia, pruritus, headache. Lymphadenopathy, often in post-cervical triangle (Winterbottom's sign), is

common; LNs are soft and non-tender; splenomegaly is rare. CNS symptoms incl. headache, change in personality, apathy, forgetfulness; psychosis (abnormal behaviour, agitation, delusions). CNS signs incl. pyramidal (focal motor weakness), extra-pyramidal (resting tremor common), and cerebellar (ataxia). Late features incl. daytime somnolence, coma, and seizures. Patients die of starvation, intercurrent bacterial infection, or convulsions.

Rhodesian trypanosomiasis

1° chancre at bite site, subsides in 2–3wks. After 1–3wks, acute severe illness with high fever, chills, malaise, severe headache, weight loss, myalgia, arthralgia. Erythematous rash (macular, papular or circinate) may occur. Disease often runs a fulminant course with multiple-organ failure and early death. CNS involvement (meningo-encephalitis) progresses rapidly and is fatal if untreated. Myocarditis causing atrial or ventricular dysrhythmia, or heart failure, may precede meningo-encephalitis.

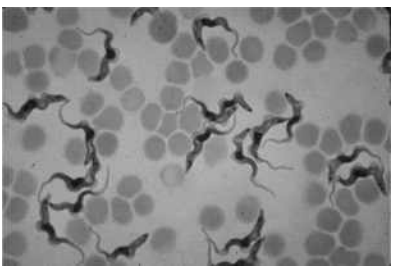

Fig. 17.16 Trypomastigote forms of *T.b. rhodesiense* on a peripheral thin blood smear. See Colour Plate 9a.

Diagnosis

Screening for Gambian HAT is by card agglutination trypanosome test (CATT), a sensitive, practical serological test. No serologic test exists for Rhodesian HAT. Direct microscopic observation of trypanosomes in LN aspirates, blood (Giemsa-stained thick smear, quantitative buffy coat, haematocrit, or mini-anion exchange centrifugation techniques) or CSF (single centrifugation) confirms diagnosis. Sensitivity of blood examination is greater in *T.b. rhodesiense* due to larger numbers of circulating trypanosomes (Fig. 17.16).

Staging disease by LP is mandatory. Findings in the CSF that indicate trypanosomal meningo-encephalitis:

- Trypanosomes.
- ↑ leukocytes (>5 per mm3) *and/or*
- ↑ total or specific (anti-trypanosomal) IgM.

Treatment

- Depends on stage of disease and if Gambian or Rhodesian.
  Note: following renewed agreement between pharmaceutical industry and WHO, drugs for HAT are being donated to WHO.

- A new oral drug, fexinidazole has been shown to be effective and safe for treatment of early- and late-stage Gambian HAT safe and effective and is an oral treatment for Gambian HAT and is registered now for use in a number of countries for first-line therapy. This drug is in clinical trials (2019–) for the treatment of both stages of Rhodesian HAT.

Gambian HAT

- Early stage: pentamidine isetionate 4mg/kg IM od for 7d.
- Late stage (first choice): eflornithine 200mg/kg IV bid for 7d, diluted in normal saline and infused over 2h, and nifurtimox 5mg/kg oral tds for 10d.
- Late stage *(alternative if nifurtimox not available or contraindicated)*: eflornithine 100mg/kg IV qds for 14d.
- Late stage *(alternative only if eflornithine not available or for treatment of relapse after eflornithine-based regimen)*: melarsoprol 2.2mg/kg/d slow IV injection, with prednisolone 1mg/kg oral od for 10 consecutive days. Use a glass syringe, or draw up and inject with a plastic syringe as soon as possible, since melarsoprol binds to plastic; very irritant, avoid extravasation (risk soft tissue necrosis). Melarsoprol is more toxic than eflornithine-based regimen and associated with up to 30% treatment failure in parts of Angola, Uganda, Central African Republic, DRC, and Sudan.

Rhodesian HAT

- Early stage: suramin 5mg/kg by slow IV injection on day 1 (test dose), followed by 20mg/kg on days 3, 10, 17, 24, and 31. In Rhodesian HAT, because of the possibility of introducing circulating trypanosomes into the CSF by the LP needle itself, it is recommended to clear the blood of visible trypanosomes with suramin prior to performing the LP.
- Late stage: melarsoprol sequential regimen (i.e. three cycles of three daily injections of 3.6mg/kg with resting period of 7–10d between each cycle) or 2.2mg/kg/d for 10 consecutive days (recently showed a similar efficacy and toxicity profile), plus prednisone 1mg/kg oral od (commence prior to melarsoprol to reduce occurrence of melarsoprol-induced encephalopathy). Eflornithine is thought to be ineffective.

See Box 17.16 for adverse effects of drugs.

Paediatric health note

HAT in neonates and infants can be due to mother-to-child transmission or early exposure to tsetse fly bites. Delayed diagnosis is common in young children due to non-specific symptoms and signs. Chronic neurodevelopmental disorders are common sequelae of late-stage HAT. Treatment regimens are similar to adults.

Public health note: prevention and control of HAT

- *Screening*: Gambian HAT control programmes rely on active case finding through systematic serologic screening by CATT of communities, and treatment of all those infected (humans are the only significant reservoir). In areas of low prevalence of Gambian HAT, integration of disease management within existing health structures is a challenge.
- *Vector control*: by tsetse fly trapping is cumbersome but effective, particularly in Rhodesian HAT control programmes.
- In outbreaks of Rhodesian HAT, a combined programme of vector control, treatment of infected cattle, and active detection and treatment of human cases should be implemented.

Challenges: improved diagnostic tools and drugs and simplified diagnosis–treatment algorithms are urgently needed.

Box 17.16 Adverse effects of drugs used for HAT

- Eflornithine: leukopenia, anaemia, thrombocytopenia, soft tissue infections, and convulsions.
- Nifurtimox: anorexia, nausea, vomiting, insomnia, mood change, psychosis, convulsions.
- Melarsoprol: encephalopathic syndrome (see later in box), polyneuropathy, severe (sometimes bloody) diarrhoea, and rash.
- Pentamidine isetionate: hypoglycaemia (frequent), hypotension, sterile abscess, and pancreatitis (rare).
- Suramin: anaphylactic shock, rash, fever, neurological, haematological, and/or renal toxicity, peripheral neuropathy.

Melarsoprol-induced encephalopathic syndrome (ES)

Occurs in 5–15% of treated patients, producing status epilepticus and coma. Mortality is ~50%. May be partially prevented by oral prednisolone 1mg/kg oral od in Gambian HAT. Onset of fever, tachycardia, headache, tremor, and conjunctival suffusion during melarsoprol treatment should be considered as a warning. Melarsoprol treatment should be stopped immediately; it can be restarted once symptoms subside. Some authorities recommend the use of high-dose dexamethasone IV (e.g. 30mg loading dose followed by 15mg every 6h for adults) for treatment of ES or impending ES.

American trypanosomiasis

American trypanosomiasis or Chagas' disease (CD) is endemic in Latin America, caused by the protozoa *Trypanosoma cruzi*, and transmitted by triatomine bugs of the reduviid family (see Fig. 17.17 and Colour Plate 9b.)

Pathogenesis

Parasites invade mesenchymal tissues (esp. heart muscle) where they persist as amastigotes with only intermittent parasitaemia, making direct detection difficult. In ~70% of adults, an adequate immune response controls infection, producing a benign chronic phase ('indeterminate form'). Persistent infection and failure to modulate the inflammatory immune response cause chronic cardiomyopathy in ~30%. GI CD is thought to result from damage to intramural autonomic ganglia during the acute phase and subsequent unmasking by age-related neural attrition.

Epidemiology and transmission

~6 million people are infected by *T. cruzi* in endemic countries of Latin America. ~1.2 million individuals have chronic Chagas cardiomyopathy. Social determinants of CD: poor housing → house infestation → risk of CD. Risk of acquiring CD while travelling is very low, but travellers should avoid poor-quality housing, and use insecticide-treated nets if sleeping in an infested house is unavoidable.

Transmission routes

- Vector transmission: via triatomine bugs (a subfamily of the Reduviidae). >140 species have been identified; five species that routinely infest or invade human dwellings are responsible for most human infections. Parasites from insect faeces enter via human nose and mouth mucous membranes, conjunctivae, or damaged skin—esp. where the insect bite is scratched and rubbed → ~30,000 new CD cases/yr.
- Transplacental transmission: ~9000 cases/yr.
- Ingestion of accidentally infected food or beverage: incl. fruit juice, occasional outbreaks of disease.
- Blood transfusion, organ transplantation: <1% blood donations are infected; blood bank screening is conducted in all endemic countries of Latin America, the USA, and Spain.
- Occupational exposure in laboratory workers.

Reservoirs

- Domestic and wild mammals are reservoirs for the parasite.

Distribution

- In the Americas, the epidemiology can be divided into two groups according to whether or not there is significant domestic and peridomestic vector-borne transmission (Table 17.10). However, these patterns have been altered by 15–25yrs of intensive domestic and peridomestic insecticide application under regional control programmes.
- With migration, CD has become a globalized disease, and individuals infected in the endemic area may be diagnosed years later in other countries. Non-endemic countries (Canada, Spain, France, Switzerland, Italy, Japan, etc.), receive migrants infected with *T. cruzi*, requiring diagnosis and treatment. In the USA, ~300,000 Latin American

immigrants are infected with *T. cruzi,* and 30,000–45,000 have clinical CD. The southern USA also has local sylvatic cycles with infected vectors and animals, incl. domestic dogs; the number of locally acquired human infections is unknown. See Fig. 17.18.

Clinical features

CD is classified into acute and chronic phases. During the chronic phase, an infected individual may be asymptomatic and have no evidence of end-organ damage (the indeterminate form) or have cardiomyopathy, GI disease, or both.

Acute

The acute phase lasts 6–8wks following infection. Infection may be subclinical, with non-specific symptoms. Local inflammation at bite site → chagoma and lymphadenopathy. If inoculation occurs via the conjunctiva, unilateral eyelid oedema may occur (Romaña's sign, see ➲ Colour plate 9c). This characteristic feature usually lasts ~1mth (c.f. bacterial conjunctivitis which usually only persists max. ~10d).

Fever occurs after an incubation period of ~2wks post infection, coinciding with parasitaemia. Rarely, the acute phase can include a maculopapular or petechial rash. There may be oedema, esp. of the face. Other features incl. hepatosplenomegaly, cardiac dysrhythmia, or failure, and rarely, meningo-encephalitis which is potentially fatal. Most congenital infections are asymptomatic. ~20–30% of infected infants present with LBW and/or hepatosplenomegaly. A few infants have more severe signs, e.g. jaundice, respiratory distress syndrome, and/or meningoencephalitis, with high risk of death.

Chronic T. cruzi infection

Diagnosis relies on positive anti-*T. cruzi* IgG serology. Parasitological and molecular tests may or may not be positive; there is usually no obvious evidence of organ damage (cardiac or GI). Normal ECG, CXR, and bowel imaging. Rigorous and sophisticated testing may detect mild changes, but no established evidence of prognostic value.

Chronic end-organ damage affects ~30% of those infected, often after decades of asymptomatic infection. Chagas cardiomyopathy occurs in all endemic areas with ↓ frequency and ↓ severity in areas under effective vector control. GI CD is much less common than cardiomyopathy, and seen almost exclusively in southern Brazil, Bolivia, Argentina, Chile, Uruguay, and Paraguay.

Cardiac

Pathology incl. conduction system deficits, esp. right bundle branch block (RBBB) and/or left anterior hemiblock, frequent ventricular arrhythmias, LV aneurysm, thromboembolism, progressive dilated cardiomyopathy, and cardiac failure in late stages. Some patients with chronic Chagas cardiomyopathy have normal LV function with only arrhythmias and conduction disorders. Ventricular arrhythmias and LV dysfunction → poor prognosis. Chest pain (usually atypical angina) is common. Dilated ventricles +/− aneurysm → mural thrombi → systemic, pulmonary, and cerebral emboli. Heart failure is exacerbated by AF; prognosis worsens as cardiac disease progresses:

- Stage 1: asymptomatic, normal ECG or non-specific findings; normal LV function on echocardiography.
- Stage II: asymptomatic or mild symptoms, characteristic ECG abnormalities (RBBB + left anterior hemiblock, first- or second-degree AV block), segmental wall motion abnormalities but no ↓ LV function on echocardiography.
- Stage III: New York Heart Association (NYHA) class I/II, more advanced abnormalities on ECG, mild to moderate ventricular dysfunction.
- Stage IV: NYHA class III/IV, atrial flutter/fibrillation, severe global ventricular dysfunction (e.g. LV ejection fraction <30%), complex ventricular arrhythmias.

Gastrointestinal

Dysphagia, regurgitation of food, chronic constipation, abdominal pain. Dysregulation of peristalsis and oesophageal sphincter relaxation, → oesophagitis, mega-oesophagus, megacolon. Complications incl. large bowel obstruction or volvulus.

Some patients have both cardiac and GI disease.

Diagnosis

In acute phase, parasites may be detectable in fresh preparations of buffy coat or stained peripheral blood specimensx (see Fig. 17.19). Serology (>2 tests) for anti-*T. cruzi* IgG +ve is the main diagnostic tool in chronic infection. Parasites may sometimes also be detected directly in wet mount or Giemsa-stained blood films (➲ Colour plate 9b) or CSF precipitate (CSF only positive in acute or reactivation disease); parasite DNA may be detected by PCR. Seropositive individuals should be evaluated for symptoms and signs of cardiac and GI disease.

Management

Acute phase

Give either:

- *Benznidazole 5–7mg/kg/d (children 10mg/kg/d)*: orally in two divided doses for 60d; max. recommended daily dose is 300mg. For adults >60kg, calculate the total dose and extend treatment period >60d. Common side effect is urticarial dermatitis (30% in 1st week of treatment), with good response to antihistamines or corticosteroids. If fever, adenopathy, or exfoliative dermatitis occurs, discontinue treatment. Other adverse effects incl. polyneuropathy (usually towards end of treatment) with pain and/or tingling in the legs, anorexia); *or*
- *Nifurtimox 8–10mg/kg*: oral in three divided doses (children 15mg/kg oral in four divided doses) for 90d; side effects: anorexia (common), abdominal pain, nausea, vomiting and weight loss; peripheral neuropathy, CNS side effects incl. insomnia, irritability, depression.

Chronic phase

Benznidazole is used, but the efficacy difficult to assess because serology takes years to decades to become negative. Trials in children 6–12yrs of age show >60% efficacy based on serology, but adult data are mixed. In the benznidazole arms of recent adult clinical trials, quantitative PCR quickly becomes negative in 85–90% of those who complete 60d treatment and remains negative during >12mth follow-up. Negative PCR is a good indicator

that the parasite load has fallen below detectable levels, but does not prove parasitological cure.

- *Symptomatic treatment*: for complications, e.g. CCF, arrhythmias (➔ Cardiac arrhythmias, p. 332), AV block, and sick-sinus syndrome or anticoagulation for systemic emboli.
- *Pacemakers*: implanted in patients with severe bradyarrhythmias.
- *Surgery*: may be required for mega-oesophagus or megacolon.
- *Heart transplantation*: in severe heart patients (CD is the third major cause of heart transplantation in Brazil).

Paediatric note: congenital *T. cruzi* infection

Transmission from infected mother to newborn children varies from 1% to 12% (median 5–6%) in different Latin American countries and should be evaluated in seropositive mothers. Congenital infection is confirmed by identification of parasites or parasite DNA in the infant's blood and/or detection of infant anti-*T. cruzi* IgG 8–9mths after birth (assuming vector and other modes of transmission excluded). Congenital CD is considered acute and requires trypanocidal treatment. Notification is mandatory.

Public health note: prevention and control of Chagas' disease

- Limit exposure to the vector: improved housing, residual insecticide spraying of houses.
- Promote the use of insecticide-treated bed nets.
- Screen donors of blood for transfusion and organ transplantation.

CD is a clear example of public policy success, with five separate large-scale vector control programmes with modern pyrethroid insecticides being implemented in last few decades in different Latin American countries. Mandatory notification of acute cases for intense epidemiological surveillance. Micro-epidemics of acute cases due to oral transmission through contaminated food, such as sugar cane juice, or açaí (*Euterpe oleracea*) fruit juice or sauce, have been described, especially in Amazon Region and in South Brazil.

Table 17.10 Grouping of countries by American trypanosomiasis transmission cycle

Countries	Argentina, Belize[2], Bolivia, Brazil[1] (outside of the Amazon), Chile[1], Colombia, Costa Rica, Ecuador, Honduras[2], Mexico, Paraguay, Peru, Uruguay[1], Venezuela, El Salvador[2], Guatemala[2], Nicaragua[2], Panama	Amazon Basin, Caribbean islands[3], USA, French Guiana, Guyana, Haiti, Jamaica, Suriname
Transmission cycles	Domestic, peri-domestic, Sylvaic	Sylvatic

[1] *T. cruzi* transmission by *T. infestans* certified as interrupted throughout Brazil, Chile, Uruguay.
[2] *T. cruzi* transmission by *R. prolixus* certified as interrupted throughout Belize, El Salvador, Guatemala, Honduras, Nicaragua.
[3] Documented in Trinidad, presumed in other islands.

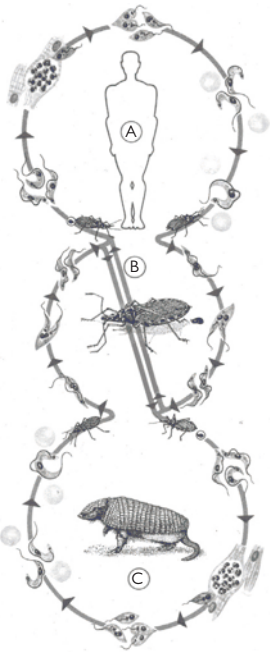

Fig. 17.17 Life cycle of *T. cruzi*. Reduviid bug (B) transmits infection via faeces when taking blood meals from animal reservoirs such as the armadillo (C) or humans (A).

Fig. 17.18 Distribution of American trypanosomiasis. *T. cruzi* infections of animals occur over a much wider range than Chagas' disease in man.

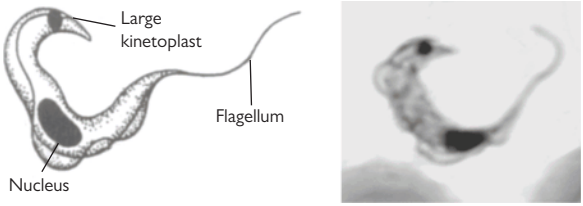

Fig. 17.19 *T. cruzi* as seen in a blood film.

Visceral leishmaniasis (kala-azar)

Introduction

Visceral leishmaniasis (VL), or kala-azar, is a severe systemic protozoan disease caused by zoonotic *Leishmania infantum* (in S America and the Mediterranean Basin; also known as *L. chagasi* in Latin America) or anthroponotic *L. donovani* (in S Asia and E Africa), transmitted to humans by nocturnal sandfly bites (Fig. 17.20). VL is endemic in areas of South America, the Mediterranean basin, Asia, and Africa (Fig. 17.21). Large deadly epidemics of *L. donovani* VL may occur in non-immune or malnourished populations. Generalized infection of macrophages → the classical clinical picture of persistent fever, splenomegaly, and anaemia and to progressive immunosuppression. VL can be confirmed by serology, including rK39 antigen-based RDTs, by microscopic examination of spleen, bone marrow or LN aspirates, or by PCR. Liposomal amphotericin B is the preferred treatment, except for *L. donovani* in E Africa where the combination of pentavalent antimonials and paromomycin is used. Treatment of VL is usually effective except in HIV co-infected or other immunosuppressed patients, who are prone to frequent relapses.

Pathogenesis

Promastigotes (flagellate forms) are present in infected sandflies' saliva; they enter human macrophages, where they transform into amastigotes (rounded forms) that proliferate, killing the host cell, infecting other cells, and spreading to the whole reticuloendothelial system (spleen, bone marrow, liver, LNs) and other tissues. Infection is often subclinical, when controlled by an efficient cell-mediated immune response. When the immune response is ineffective, clinical VL develops. Latent infections can reactivate during immunosuppression.

Transmission

Transmission is by the nocturnal bite of female *Phlebotomus* and *Lutzomyia* sandflies (Fig 17.20). Dogs are the major reservoir of *L. infantum* in the Mediterranean basin and Brazil, where the zoonotic form of VL primarily—but not exclusively—affects children and immunosuppressed individuals (see Fig. 17.21). Humans are the main reservoir of *L. donovani*, a more virulent *Leishmania* species that can affect all age groups. Patients with post-kala-azar dermal leishmaniasis (PKDL) are medium-term reservoirs of *L. donovani*. Transmission by blood transfusion or organ transplantation, and from mother to child (congenital VL), occasionally occur. (Fig 17.22).

Clinical features

Following an incubation period of several weeks or months, patients present with persistent fever, accompanied by night sweats, headaches, cough, epistaxis, and abdominal pain/distension due to the enlarged spleen. Enlarged 2–3cm lymph nodes (esp. inguinal) are commonly noticed in E Africa. Darkened skin is noticed in <20% of patients in Asia—means 'black disease' in Hindi. Weight loss, cachexia, anaemia, and fatigue gradually worsen. Epistaxis is characteristic. In the absence of treatment, death occurs, usually from superimposed infections like pneumonia, sepsis, tuberculosis, measles, or malaria; or from major bleeding; or from anaemic heart failure.

Main differential diagnosis Malaria, disseminated TB, brucellosis, enteric fever.

Diagnosis

Several diagnostic confirmatory tools have been validated in clinical suspect patients, e.g. with ≥2wk fever and splenomegaly:

- *Serology*: ELISA and IFA tests have good diagnostic performance but are not designed for field use. The semi-quantitative direct agglutination test (DAT) has high sensitivity and specificity in all endemic areas. Rapid diagnostic tests (RDTs) detecting antibodies against recombinant K39 antigen allow for decentralized diagnosis. Whereas the specificity of rK39 RDTs is high (>90%) in all endemic areas, their sensitivity varies with the geographic location, being rather insensitive (<85%) in E Africa.
- *Parasitology/PCR*: microscopic examination of Giemsa-stained smears of spleen aspirate is ≥95% sensitive but the procedure requires expertise. Sensitivity is lower (60–80%) with aspirates from LN or bone marrow. Sensitivity is markedly improved by culture or PCR.

Management

VL treatment is both supportive (e.g. nutrition, blood transfusions, antibiotics) and specific (anti-leishmanials). Superimposed bacterial infections should be treated with a low index of suspicion. The choice of antileishmanial drugs and regimen depends on the geographical area, presence of immunosuppression (Box 17.17), and availability of drugs:

L. infantum endemic areas

- Liposomal amphotericin B (LAmB): 18–21mg/kg total dose divided in 2–7 daily infusions.
- Alternative: IM or IV pentavalent antimonials (Sbv) 20mg/kg/d for 30d; there is no upper limit on the daily dose; meglumine antimoniate and sodium stibogluconate are equivalent.

L. donovani in South Asia

- LAmB: 10mg/kg single dose or 15mg/kg total dose divided in three daily infusions.
- Alternative: oral miltefosine (dosage adjusted to body weight) + IM paromomycin 15mg/kg/d for 10d.

L. donovani in East Africa

- IM or IV pentavalent antimonials (Sbv) 20mg/kg/d + IM paromomycin 15mg/kg/d for 17d.
- Alternative: LAmB 30–40mg/kg total dose divided in 6–10 daily infusions; used as preferred treatment for patients at ↑ risk of death with Sbv: age <2yrs or ≥45 years, severe malnutrition (BMI <13kg/m2), severe anaemia (Hb <6g/dL), jaundice, concomitant HIV or TB.

Main drug-specific side effects:

- LAmB: (mild) infusion-related reactions, renal toxicity, hypokalaemia.
- Sbv: arthralgias, pancreatitis, cardiac arrhythmias (may be fatal).
- Paromomycin: pain at injection site, (mild) renal toxicity, ototoxicity.
- Miltefosine: (mild) vomiting, renal or hepatic toxicity, teratogenicity (effective contraception during and ≥5mths after treatment).

Clinical improvement should be evident in 7–10d. Response can be monitored by ↓ fever, ↑ Hb, and ↑ spleen size. A parasitological response is shown by a negative test-of-cure (splenic, bone marrow, or LN aspirate). Clinical follow-up for 6–12mths is important to detect relapses, which should be <5%.

Box 17.17 VL–HIV co-infection

- Co-infections have been reported in all VL endemic areas, but are particularly prevalent in northern Ethiopia.
- HIV and VL have a synergistic effect to ↓ cellular immunity, → fewer subclinical and more overt infections and an accelerated progression of HIV disease.
- The VL clinical features in HIV+ve patients are similar to non-HIV patients but some HIV+ve patients present with atypical features, e.g. skin, pulmonary, or intestinal involvement.
- There is ↓ sensitivity of most serological tests (the DAT being spared), but ↑ sensitivity of parasitology and PCR (due to ↑ parasite load).
- Pentavalent antimonials are contraindicated due to significant (up to 25%) risk of death; patients should be treated with LAmB 40mg/kg total dose. Clinical trials are underway to assess the efficacy and safety of LAmB combined with miltefosine.
- Relapses are frequent and are only partially prevented/delayed by 2° prophylaxis with IM or IV pentamidine isethionate 4mg/kg once a month and early introduction of ART.

Public health note

- Commercial vaccines are available to prevent VL in dogs but none are yet available for humans.
- In areas of zoonotic VL, deltamethrin-impregnated dog collars ↓ transmission of *L. infantum*.
- In the *L. donovani* S Asian focus, the governments of India, Nepal, and Bangladesh are implementing an elimination programme aiming at ↓ the VL annual incidence to <1/10,000 at subdistrict level. Activities are based on early detection and treatment of cases and vector control by indoor residual spraying.
- In the *L. donovani* E African focus, transmission to humans mainly occurs outdoors. While the use of insecticide-treated bed nets and peri-domestic spraying may have some limited effect on transmission, VL cannot be controlled effectively in this region and recurrent epidemics occur, which are magnified by civil unrest and population displacements.

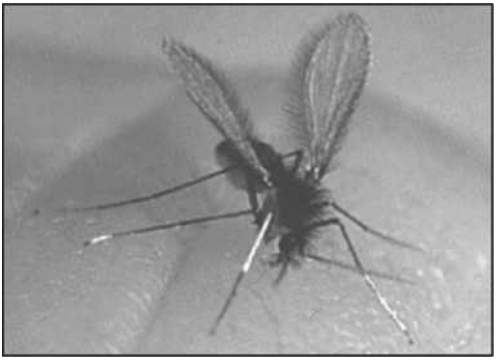

Fig. 17.20 The female phlebotomine sandfly is about half the size of a mosquito and feeds nocturnally. Several species transmit visceral or cutaneous leishmaniasis. Reproduced with permission from Centers for Disease Control and Prevention's Public Health Image Library (PHIL), ID: #10277. Image is in the public domain.

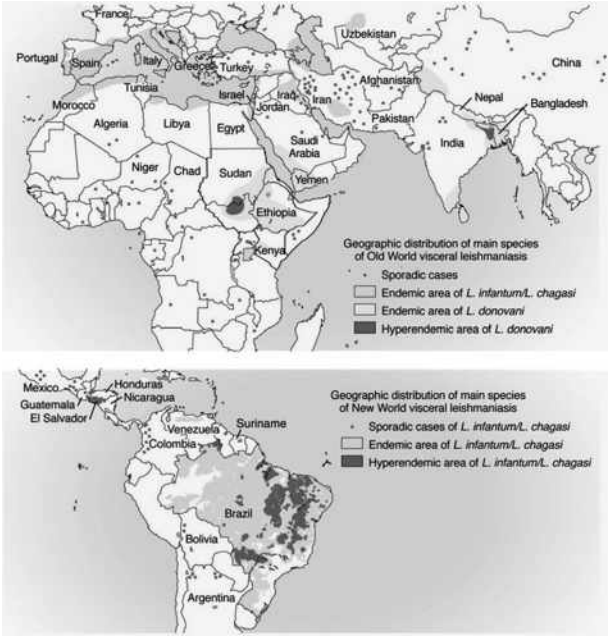

Fig. 17.21 Geographic distribution of visceral leishmaniasis.

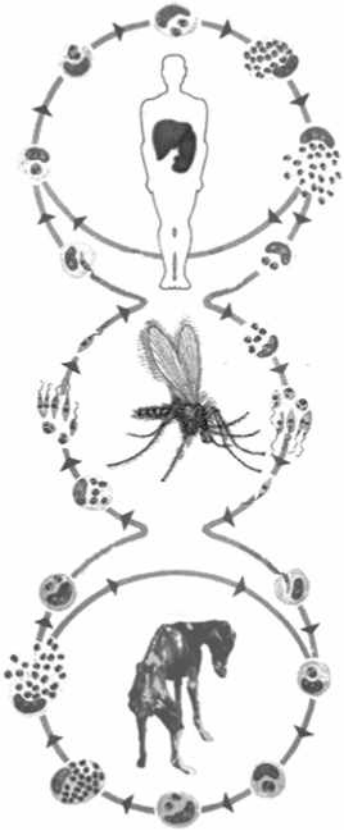

Fig. 17.22 Life cycle of visceral leishmaniasis. Adapted from Piekarski, G, Medical Parasitology in Plates, 1962, with kind permission of Bayer Pharmaceuticals.

Infectious mononucleosis

Infectious mononucleosis (glandular fever) is classically caused by 1° infection with EBV infection. A glandular fever-like illness is also caused by acute HIV, CMV, and *Toxoplasma gondii* infection.

Transmission

EBV (human herpesvirus 4) is usually transmitted orally via saliva. It establishes infection in the oropharynx and circulating B cells. Latent EBV infection persists, and intermittent viral shedding occurs spontaneously and esp. during febrile illnesses, e.g. malaria. In resource-poor regions, >90% children are infected with EBV by 5yrs, but show little clinical illness. The clinical picture of infectious mononucleosis is common in adolescence/adults, of whom ~50% develop clinical illness when infected.

Clinical features

Symptoms/signs

Classically fever, pharyngitis, lymphadenopathy, and fatigue. The grey necrotic slough on tonsils needs to be distinguished from diphtheria. Splenomegaly/hepatosplenomegaly, hepatitis, thrombocytopenia, palatal petechiae, and morbilliform rash may occur (rash more common following ampicillin or amoxicillin administration).

Complications

Splenic rupture (spontaneously or after minor trauma) is uncommon but may be fatal. Upper airway obstruction may occur due to tonsillar and adenoidal enlargement. Encephalitis, hepatitis, myocarditis, pericarditis, pneumonitis, haemolytic anaemia, and nephritis are rare.

Latent EBV is implicated in some malignancies, including:

- Burkitt's lymphoma, common in equatorial Africa and Papua New Guinea; linked to intense malaria transmission.
- Nasopharyngeal carcinoma, esp. in SE Asia, China, and parts of N and E Africa; linked to environmental/dietary factors.
- Hodgkin's lymphoma.
- B-cell lymphoproliferative disease in the immunocompromised.
- Oral hairy leukoplakia, CNS and other lymphomas in HIV.

Diagnosis

- Lymphocytosis, atypical lymphocytes, mild ↓ platelets, ↑ transaminases.
- IgM heterophil antibody tests (Paul Bunnell, Monospot) commonly used (limited value in children <4yrs). Presence of IgM antibody against EBV viral capsid antigens (VCA) in absence of IgG antibody against EBV nuclear antigen 1 (EBNA) confirms acute infection.

Management

- *Supportive*: hydration, analgesia, +/− mild NSAIDs.
- Avoid contact sports for at least 4wks after symptom onset (splenic rupture rarely reported after 4wks).
- Consider corticosteroids for impending airway obstruction.
- Avoid amoxicillin in infectious mononucleosis as it precipitates a morbilliform rash in 70–90% of patients.
- Aciclovir is of no proven clinical benefit and is not recommended.

Measles

Measles is a highly contagious viral (paramyxovirus) disease, which is vaccine preventable, and can cause severe disease and death, particularly in children.

Epidemiology

Measles immunization prevented ~20.3 million deaths between 2000 and 2015 (a 79% reduction in annual deaths) but still caused >130,000 deaths in 2015. All WHO Regions have the goal of measles elimination goals by 2020; the Americas successfully interrupted endemic transmission in September 2016. Only eight of the 24 known measles virus genotypes have been detected since 2009. Unless 95% immunity is achieved in each birth cohort, measles will continue to discover immunity gaps and cause outbreaks.

Transmission

- Only humans are infected, mainly by respiratory droplets and small particle aerosols that can remain airborne for 2h. Direct contact with respiratory secretions is another route.
- A measles case is infectious from 4d before to 4d after onset of the rash.
- On average, 9–18 non-immune people can be infected by a single measles case.
- Incubation period from exposure to onset of febrile symptoms is 10d (14d to onset of rash) but may be as long as 23d.

Clinical features

Measles should be considered in the differential diagnosis of any patient with fever and erythematous rash.

Fever

Fever >38°C accompanied by at least one of the three Cs: cough, coryza, or conjunctivitis, with fever persisting after the appearance of rash.

Rash

Distinctive, erythematous, non-vesicular maculopapular rash appears on day 3 or 4 of fever. As well as having rash, patient looks ill, miserable, and the three Cs are common. Rash begins on face and behind ears, within 24–36h the rash spreads down trunk → extremities (palms and soles rarely often involved). Begins to fade after 3–5d, initially to a purplish hue and then brown/black lesions with desquamation esp. in malnourished children. Koplik spots (grey-white spots surrounded by erythema on the buccal mucosa) may appear 24–48h before rash onset, but are often missed.

Diagnosis

Measles should be suspected in all cases of:

- Fever.
- Generalized maculopapular rash.
- Especially if at least one of:
  - Cough.
  - Coryza.
  - Conjunctivitis.
- Particularly where there is no prior history of confirmed measles disease or two appropriately timed doses of measles vaccination.

Laboratory confirmation

As measles elimination is approached, it is important to attempt to confirm all sporadic suspected measles cases and chains of transmission, by serology or detection of viral RNA by PCR. An epidemiologically confirmed measles case is a suspected measles case, although not laboratory confirmed, with onset of rash 7–23d after contact with a laboratory- or epidemiologically confirmed measles case.

- Serology: measles-specific IgM (unreliable during first 72h after rash onset) or fourfold ↑ in measles IgG antibody titres between acute and convalescent specimens. An adequate specimen for antibody detection is ≥0.5mL of sera or ≥3 fully filled circles of dried blood on a filter paper, or oral fluid collected <28d after rash onset.
- PCR: from throat or nasopharyngeal swabs or urine samples; PCR is +ve from 1st day of rash up to 14d.
- Virus isolation: measles virus can be isolated from nasopharynx or conjunctival swabs, respiratory secretions, and urine.

Complications of measles

Measles complications occur commonly but particularly in immunocompromised (HIV+ve), malnourished (protein-calorie and vitamin A deficiency), pregnant women, and young children (<5yrs), with up to 20% case fatality in those aged <1yr.

Measles causes local tissue damage and ↓ cellular immunity; this predisposes to infection and persists for ~6–8wks after the acute illness. Pneumonia and diarrhoea are the most common complications and account for ↑ case fatality.

Respiratory tract infection

- Respiratory symptoms are characteristic of measles and assumed to be 1° viral pneumonitis.
- Giant cell pneumonia and 2° bacterial pneumonia (*Staph. aureus*, *Strep. pyogenes*, *Strep. pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *Pseudomonas* spp.) are the leading causes of measles-associated deaths.
- Otitis media, with attendant hearing loss, may also follow 1° measles infection.

Gastrointestinal complications

Diarrhoea can occur within a few days of rash onset, and → ↑ case fatality and ↑ malnutrition.

Neurological complications

Encephalitis occurs in 1/1000 cases and 25% of affected children have neurodevelopmental sequelae, with a 15% case fatality.

- Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disease occurring 2wks after rash. Presents with fever, seizures, and other neurological symptoms.
- Measles inclusion body encephalitis (MIBE) is progressive measles virus infection of the brain in patients with ↓ cellular immunity with neurological deterioration and death within months of acute infection.
- Sub-acute sclerosing panencephalitis (SSPE) is a fatal, neurodegenerative disease which occurs in 1/10,000 to 1/100,000 cases, 5–10yrs after the primary illness.

- *Eye complications*: keratoconjunctivitis may → blindness, esp. in children who are vitamin A deficient.
- Other common complications: incl. malnutrition, mouth ulceration, premature delivery, and spontaneous abortion.

Management

There is no specific antiviral treatment, so management includes: supportive care, identification and management of complications, and preventing spread through careful infection control measures (Box 17.18).

- Ensure adequate nutrition, hydration, and support, incl. education about complications.
- Give vitamin A (dose and regimen, ➲ Vitamin A deficiency, p. 658): this corrects vitamin A deficiency, ↓ severity of illness, and ↓ case fatality.

If specific symptoms/signs or conditions are present:

- Give symptomatic relief from high fever with paracetamol.
- Treat eye infection (cornea cloudy or pus draining from eyes) with topical antibiotics.
- Manage diarrhoea/dysentery and dehydration as on ➲ General management of dehydration, p. 236.
- Broad-spectrum antibiotics for treatment of pneumonia.

Box 17.18 Prevention of measles

- Give first dose of measles-containing vaccine (MCV) at 9–12mths of age.
- MCV can be given as early as 6mths of age, e.g. during outbreaks, for internally displaced populations and refugees, HIV-infected children, and children at high risk of contracting measles, e.g. travel into outbreak-affected area. This is an additional MCV dose, and does not replace the 9–12mth dose.
- HIV-infected children should be revaccinated against measles following immune reconstitution with ART.
- Second MCV vaccine dose should be administered to all children in the 2nd year of life. This will → life-long protection in most people.
- Identify children who have missed out on immunization at school entry.
- Measles outbreaks can be devastating in refugee settings. Urgent measles immunization to unimmunized displaced people is a public health priority.
- Measles vaccine is a live attenuated virus vaccine with an excellent safety record. It is contraindicated in pregnancy. It should be given routinely to asymptomatic, HIV-infected children, adolescents, and young adults. Those with severe clinical symptoms of HIV infection are contraindicated for vaccination.
- Measles surveillance is a public health priority, allowing prompt recognition and investigation of outbreaks and immunity gaps in certain age-groups or subpopulations.

Arboviruses and zoonotic haemorrhagic fever viruses

Arboviruses are transmitted to humans by an arthropod vector, e.g. mosquito, tick, fly, flea, or midge. The majority are zoonoses. Most arboviruses can cause a mild self-limiting fever, or a febrile syndrome with myalgia, arthralgia, rash, encephalitis, or meningoencephalitis. Disease can however be severe and some arboviral infections, such as CCHF, Rift Valley fever (RVF), dengue, and yellow fever, can be accompanied by haemorrhagic symptoms. Similarly, infection with Lassa, Ebola, and Marburg viruses, which are zoonotic but not arboviruses, can also cause bleeding. The term 'viral haemorrhagic fevers (HFs)' has been used for a diverse group of viral infections where bleeding may be observed, but is misleading since haemorrhage occurs only in a minority (see Fig. 17.19).

Ebola, Marburg, Lassa, and some arboviruses (e.g. CCHF virus) are biosafety level 4 (BSL-4) category viruses due to the high case fatality rate and the potential for human-to-human transmission. Interhuman transmission can occur through contact with bodily fluids, usually via caring for infected individuals without appropriate infection prevention and control (IPC) measures. These viruses are associated with a high risk of nosocomial infection, with healthcare workers and laboratory workers at particular risk. Stringent IPC procedures must be used when dealing with suspected HF cases and their body fluids (see 'Public health note'). Early symptoms are often non-specific, so clinical suspicion is often low outside of an outbreak. A high index of suspicion is needed in endemic areas, and it is essential that IPC precautions are adhered to in all healthcare facilities.

In an endemic area, any patient with fever and bleeding should be considered to have HF until proven otherwise. Bleeding can be subtle. Patients should be carefully examined for bleeding gums, conjunctival bleeding, oozing from venepuncture sites, and petechiae. History taking, depending on the virus, should focus on exposure to animals, tick bites, illness among contacts, travel history, visits to natural healers, burial attendances and contact with corpses. For viruses such as Ebola and Marburg, where interhuman transmission is the main mechanism of spread, an index case often infects household contacts and relatives. A cluster of illness among family members should raise alarm bells. Pregnant patients can present with complications of pregnancy (e.g. bleeding, premature rupture of membranes, fetal death), sometimes without fever. A high index of suspicion is therefore needed in pregnant patients. In non-endemic areas it is important to consider recent travel to endemic areas.

Table 17.11 outlines the geographical distribution, vector, mode of transmission, and biosafety level (BSL) for arboviruses and zoonotic HF viruses.

Table 17.11 Classification of arbovirus infections and zoonotic haemorrhagic fever viruses

Family, disease	Geographic distribution	Vector/mode of transmission	Natural host	BSL
Flaviviruses				
Japanese encephalitis	Asia, Western Pacific	*Culex* mosquito	Birds, (pigs amplifying host)	3
St. Louis encephalitis	Americas	*Culex* mosquito	Birds	3
Murray Valley encephalitis	Australia, Papua New Guinea	Mosquito, mainly *Culex*	Birds	3
Yellow fever	Africa, South and Central America	*Aedes* and jungle mosquitoes, anthroponotic^	Primates	3
Dengue (DEN 1–4)	Africa, the Americas, the Eastern Mediterranean, SE Asia, the Western Pacific	*Aedes* mosquito, anthroponotic^, human blood, breast milk	Humans (and non-human primates)	3
Kyasanur Forest disease	S Asia	*Ixodid* (hard) ticks	Small forest mammals	3
Kunjin	Australia, Indonesia, Asia	*Culex* mosquito	Birds	3
West Nile	Africa, Europe, Asia, Middle East, N and Central America	*Culex* mosquito	Birds	3
Tick-borne encephalitis	Russia, Asia, Europe, Scandinavia	*Ixodid* (hard) ticks, non-pasteurized milk, human blood, breast milk	Small mammals	3
Alphaviruses				
Chikungunya	Africa, Americas, Asia, Europe	*Aedes* mosquito, anthroponotic^	Humans, primates	3
O'nyong'nyong	Africa	*Anopheline* mosquito	Humans (other unknown)	2
Venezuelan equine encephalitis	S and Central America	Mosquito	Horses	3
Eastern equine encephalitis	N and S America, the Caribbean	*Aedes*, *Culex*, and *Coquillettidia* mosquitoes	Horses	3
Western equine encephalitis	N and S America	*Culex* and *Culiseta* mosquitoes	Horses	3

Family, disease	Geographic distribution	Vector/mode of transmission	Natural host	BSL
Ross River fever	Australia, S Pacific	*Culex* and *Aedes* mosquitoes	Kangaroos, wallabies, other mammals	2
Coltiviruses				
Colorado tick fever	Western USA, Canada	Wood tick	Rodents and small mammals	2
Bunyaviruses				
Rift Valley fever	Africa, Middle East	Mosquito (mostly *Aedes*), animal blood/tissue	Domesticated livestock	3
La Crosse encephalitis	USA, Canada	*Aedes triseriatus* mosquito	Small forest mammals	3
Haemorrhagic fever with renal syndrome and Hantavirus cardiopulmonary syndrome*	Far East, Europe	Rodent bite/urine/faeces	Rural rodents	2/3
Crimean–Congo haemorrhagic fever	Eastern Europe, Asia, Africa	*Ixodid* (hard) ticks, animal blood, human body fluids	Small wild mammals, domestic livestock	4
Severe fever with thrombocytopenia syndrome	China, Japan, Korea	*Haemaphysalis longicornis* ticks	Domestic livestock	3
Toscana virus and other sandfly fever viruses	Southern Europe, Africa, Asia, the Americas	Phlebotomine sandfly	Unknown	2
Arenaviruses				
Lassa fever	Western Africa	Rodent urine/faeces, human body fluids	*Mastomys* rodent	4
South American HFs**	South America	Rodent saliva/urine, human body fluids	Rodents	4
Filoviruses				
Ebola and Marburg	Sub-Saharan Africa	Human body fluids, animal blood/tissue	Unknown	4

BSL, biosafety level.

^ Anthroponotic: human–vector–human transmission.
* Hantaan, Seoul, Dobrava, and Puumala viruses.
** Argentine, Bolivian, Venezuelan and Brazilian HF, caused by Junin, Machupo/Chapare, Guanarito, and Sabia viruses, respectively.

Public health note

Always adhere to IPC procedures when dealing with patients with febrile illness. For viruses that can be spread via contact with bodily fluids (e.g. Ebola, Marburg, Lassa, Junin, Machupo, CCHF) consult local experts, WHO, or CDC immediately to advise on infection control and diagnosis. See the following list for general guide. More detailed infection control advice is available at: http://www.cdc.gov/vhf/ebola/clinicians/evd/infection-control.html.

Infection control precautions

- Isolate patient immediately.
- Set up at least two areas or wards: one for patients meeting case definition for suspect cases; and one for confirmed patients. High-risk patients, i.e. 'probable' cases, should be isolated in a separate area if space and resources allow.
- Wear PPE in isolation areas and when in contact with patients, their clothing, belongings, or body fluids.
- Use two sets of gloves, a coverall that passes ASTM F1671 (13.8 kPa) or ISO 16604 (≥14kPa), apron, boots, eyewear, hood, and a mask (FFP3 or N95). PPE must completely cover clothes, skin, and mucous membranes.
- Reinforce and monitor the use of universal precautions in non-isolation areas of the health facility.
- Putting on (donning) and taking off (doffing) PPE should always be supervised by a colleague. There are different procedures for doffing PPE; whichever is chosen, use the same systematic method to avoid errors during doffing; ensure this is standardized through the use of Standard Operating Procedures (SOPs).
- Use extra precautions with pregnant patients during delivery (e.g. elbow-length gloves, delivery from side of patient).
- Always enter the isolation area with a 'buddy' for safety reasons.
- 0.5% hypochlorite solutions should be used when cleaning gloves between patients, but gloves should be dried before patient contact. 0.05% hypochlorite solution should be used for hand hygiene.
- Handle needles and other sharp instruments safely. Never recap needles. Dispose of needles, syringes, and other sharp instruments in puncture-resistant containers. Never re-use needles.
- Report all instances of PPE breaches to the person responsible for occupational health in your organization. All organizations should have SOPs in place to manage PPE breaches.
- In the case of a needlestick injury or mucous membrane exposure, seek expert advice regarding post-exposure prophylaxis (e.g. CDC, Public Health England, or WHO).
- Avoid sharing equipment between patients. Designate equipment for each patient, if supplies allow. If sharing equipment is unavoidable, make sure it is not reused by another patient until it has been cleaned, disinfected, and sterilized properly.
- Disinfect all spills, equipment, and supplies safely. Use disinfectant sprayers and 0.5% hypochlorite solutions.
- Dispose of all contaminated waste, including human remains, by incineration or burial in a safe, secure way (including safe burial of corpses).

- Set up a triage system at the entrance of healthcare facilities. Patients meeting the case definition should be isolated until they test negative for the disease.
- Determine case's places of residence and activities over last 3wks; search for unreported or undiagnosed cases.
- Establish surveillance for individuals at risk—all close contacts <3wks since onset of illness, and healthcare workers and laboratory staff that have come in contact with patients or specimens without full PPE. Surveillance comprises body temperature measurement twice-daily until 3wks after last possible exposure.
- If a contact develops a fever >38°C or otherwise meets the case definition, they should be hospitalized immediately in isolation.
- Provide appropriate information to families and the community about the prevention of infection and the care patients will receive in healthcare facilities. There may be fear/suspicion of healthcare facilities and organizations during outbreaks; early involvement of social scientists, anthropologist and health promotion specialists is recommended to engage and inform communities.

Ebola and Marburg virus diseases

Ebola and Marburg viruses are BSL-4 filoviruses. Although both may cause a viral haemorrhagic fever (VHF) syndrome, most patients do not bleed so the terms Ebola virus disease (EVD) and Marburg virus disease (MVD) are favoured.

There are six species of Ebola virus: Zaire, Sudan, Bundibugyo, Tai Forest, Bombali, and Reston. Mortality is 40–90%, depending on the species, size of the outbreak, and level of healthcare. The majority of outbreaks have been caused by the Zaire strain. Reston and Bombali are not known to cause symptomatic infection in humans.

There is one species of Marburg virus, and <500 confirmed cases of MVD since 1967. The mortality of MVD is ~50%.

Epidemiology and transmission

Bats are thought to be the reservoir for EVD and MVD. Primates and other mammals may also be infected. Outbreaks usually start after infected animals are handled or consumed, with 2° cases among relatives and HCWs caring for sick individuals, through contact with body fluids; or through contact with corpses at burials. Nosocomial infections are frequent early in outbreaks, before identification of the viruses and systematic use of PPE. Vertical transmission can occur, as can sexual transmission and transmission via breastmilk.

Outbreaks of EVD have occurred in Central and W Africa—the majority in the DRC and Uganda. A large outbreak of EVD occurred in Sierra Leone, Liberia, and Guinea in 2014–2016, with >29,000 patients affected and 11,000 deaths.

Outbreaks of MVD have to date been smaller and less frequent than EVD, and have mostly occurred in the DRC, Uganda, and Angola.

Clinical features

The clinical features of 'VHF' syndromes are summarized in ➲ Table 17.12, p. 750. EVD and MVD result in similar symptoms. The incubation period is 2–21d. Almost all patients experience fever. Headache, myalgia, vomiting, diarrhoea, and abdominal pain are common. Vomiting and diarrhoea usually start within 6d of symptom onset. Diarrhoea may be severe and → dehydration and shock. A rash can occur but can be difficult to detect on dark skin. Confusion may occur due to dehydration, hypoglycaemia, and renal failure. A few patients will develop meningoencephalitis. Chest pain may result from oesophagitis, myocarditis, or pericarditis. Conjunctivitis occurs in some.

Bleeding is seen in some patients, with petechiae, bruising, mucosal bleeding, and bleeding from puncture sites. A minority of patients will develop frank haemorrhage, usually late in illness. Vascular leak may occur → peripheral oedema and respiratory distress, often complicated by hypoalbuminemia.

Pregnant patients can present with 'atypical symptoms', such as abdominal pain, back pain, or premature rupture of membranes without fever or other typical signs. Pregnancy is associated with higher mortality, and miscarriage and stillbirth are common.

Patients either recover or die around the 2nd week of illness. Death is usually a result of renal failure, respiratory failure, encephalitis, bleeding, or shock.

Diagnosis

Virus may be detected in body fluids (usually blood) by nucleic acid testing (NAT; e.g. reverse transcription-PCR). NATs are usually positive from 3d after symptom onset; repeat testing may be needed in patients with <3d symptoms. Rapid antigen tests are available.

Laboratory findings, like the clinical features, are non-specific; they include leukopenia, thrombocytopenia, ↑ serum transaminase, as well as renal and coagulation abnormalities. Other laboratory findings incl. hypoalbuminaemia, hypoglycaemia, and ↑ amylase levels. Platelet levels rarely drop below 50,000/mm³. Transaminases are often in the hundreds and can peak in the thousands. Electrolyte disturbances are common due to vomiting and diarrhoea.

Management

Several 1st line antiviral agents are under investigation. A number of mABs have been registered for treatment.

Patients with mild diarrhoea can be managed with ORS. Large volume diarrhoea may require up to 8L or more of IV fluids per day. Fluid management can be challenging due to vascular leak and should be guided by regular clinical assessments; consider urethral catheter to monitor urine output. Overhydration can → respiratory failure.

Treat fever with paracetamol, nausea/vomiting with antiemetics, and pain with analgesics, including opiates for severe pain. Avoid NSAIDs due to risk of renal failure. The role of antidiarrhoeal agents is unclear.

Invasive haemodynamic monitoring, respiratory support, and renal replacement therapy are appropriate if indicated and possible. These procedures should only be performed by clinicians who have been specifically trained in how to do so in PPE. In general, non-invasive ventilation should be avoided due to the risk of aerosol production.

The management of bleeding should be guided by clotting results. In the absence of coagulation tests, whole blood clotting time can be used (➲ Snake bite, p. 828), but patients should be closely monitored for signs of pulmonary oedema.

Test all patients for malaria co-infection. 2° bacterial infection may be a late complication—treat suspected sepsis with antibiotics, e.g. IV ceftriaxone.

Test all women of child-bearing age for pregnancy. Complications of pregnancy are common, and obstetric advice should be sought.

Convalescence

EVD may be followed by prolonged convalescence, during which symptoms include fatigue, myalgia, arthralgia, insomnia, headache, and memory impairment. Severe complications incl. uveitis, hearing loss, and depression. These can develop within weeks or months of recovery. Patients should be followed up after discharge to monitor for these complications. Advise patients to use barrier contraception for at least 6mths after infection to prevent sexual transmission, due to the risk of persistent virus in genital fluids.

Crimean–Congo haemorrhagic fever

Crimean–Congo haemorrhagic fever (CCHF) is caused by CCHF virus, a BSL-4 bunyavirus. The reservoir is domestic livestock. Transmission to humans occurs by ticks, and by contact with body fluids of infected animals. Nosocomial and vertical transmission also occur.

Most cases occur in south-eastern Europe and western Asia, but CCHF is also reported in several African countries. Seasonal peaks usually occur in May–September.

The incubation period is usually 1–3d (up to 13d), following a tick bite. Patients may or may not report tick exposure. Clinical illness ranges from mildly symptomatic to frank bleeding and organ failure. Most patients have fever; myalgia, N&V are common. Patients either recover after ~7d or → to severe disease. Mortality is ~10%, but varies between countries.

Diagnosis

Diagnosis is primarily by NATs, which are most sensitive. Due to variations in the strain of the virus, maximal sensitivity is provided by a combination of NAT and serology.

Treatment

Treatment is mainly supportive. Some centres use ribavirin although its effectiveness is unclear. Invasive ventilation, vasopressors, and renal replacement therapy are appropriate if these can be safely performed. Give platelet transfusions to keep platelets >50,000/mm^3 if active bleeding (>20,000/mm^3 in absence of bleeding).

Rift Valley fever

Rift Valley fever (RVF) is caused by a bunyavirus. Transmission occurs via bites from infected mosquitoes or contact with body fluids of infected mammals. Outbreaks are most common in East and West Africa, esp. after heavy rains when ↑ mosquito numbers → infection of domesticated animals. Spill over into the human population mainly occurs via handling of infected animals.

Symptoms are non-specific. Fever, myalgia, headache, and GI symptoms are common (Table 17.12).

Diagnosis

Diagnosis is by NAT (e.g. reverse transcription-PCR) and serology.

Treatment

Treatment is supportive. Overall mortality is usually <1%, but has reached ~25% in hospitalized cases in some smaller outbreaks.

Table 17.12 Clinical features of viral haemorrhagic fever syndromes

Disease	Incubation (days)	Case infection ratio	Case fatality rate	Features of severe disease
Arenaviridae				
South American HFs	7–14	>50%	15–30%	Overt bleeding and shock; CNS involvement (dysarthria, intention tremor) common
Lassa fever	5–16	Mild infection common	2–15%	Prostration and shock; fewer haemorrhagic or neurological manifestations cf. S American HF
Bunyaviridae				
Rift Valley fever	2–5	1%	50%	Bleeding, shock, anuria, jaundice; encephalitis and retinal vasculitis occur but are distinct from HF syndrome
Crimean–Congo HF	1–13	20–100%	15–30%	Most severe bleeding and bruising of all the HFs
HF with renal syndrome (Hantavirus)	9–35	>75%	5–15%	Febrile stage followed by shock and renal failure; bleeding at all stages
Filoviridae				
Marburg or Ebola virus disease	3–16	High	25–90%	Most severe of HFs; marked prostration; maculopapular rash common
Flaviviridae				
Dengue	➲ p. 756			
Yellow fever	➲ p. 761			
Kyasanur Forest disease	3–8	Variable	0.5–9%	Typical biphasic illness — fever and haemorrhage followed by CNS involvement

Lassa fever

Epidemiology and transmission

Lassa fever is caused by an arenavirus which is endemic in W Africa. Lassa virus is a BSL-4 virus. The animal reservoir for Lassa virus is the multimammate rat *Mastomys natalensis*.

Transmission to humans occurs via contact with infected rodent urine and faeces, or consumption of infected rodents. Person-to-person transmission can occur through contact with body fluids but is relatively rare outside hospital settings.

Annual seasonal outbreaks of Lassa fever occur throughout W Africa, with peaks in January–March. Incidence is highest in Nigeria, Sierra Leone, Liberia, and Guinea, with cases reported in Benin, Ghana, Mali, Côte d'Ivoire, and Burkina Faso. Serological studies from the 1980s suggested that there may be hundreds of thousands of infections per year, most being asymptomatic or mildly symptomatic.

In hospitalized patients, mortality averages 30%. Pregnancy is associated with ↑ mortality.

Clinical features

The incubation period is 5d to ~3wks. Although Lassa virus can cause a VHF syndrome, most patients do not bleed.

Most infected individuals have mild symptoms, consisting of low-grade fever, malaise, and headache. In patients presenting to hospital, vomiting, diarrhoea, myalgia, chest pain, and abdominal pain are common. Abdominal pain can mimic an acute abdomen, and HCWs have been infected during surgery. Some patients develop pharyngitis with associated cervical lymphadenopathy.

Severe infection can → vascular leak → facial swelling, pulmonary oedema, and shock. Facial swelling, pharyngitis, or unexplained bleeding in a Lassa endemic zone, esp. during the Lassa season, should raise concern. Meningoencephalitis occurs in a few patients and can be the main presenting syndrome.

Diagnosis

Diagnosis is by detection of virus in blood by NAT. A rapid antigen test is also available. Laboratory findings are non-specific. Renal failure and hepatitis are common and associated with a worse prognosis. Thrombocytopenia can occur but platelet levels rarely drop below 100,000/mm^3. Coagulation abnormalities are not usually seen in Lassa fever, and bleeding is thought to be 2° to platelet dysfunction.

Management

Treatment consists of IV ribavirin, the only antiviral agent currently available, and supportive care.

Give a loading dose of 33mg/kg ribavirin; followed by 16mg/kg qds for 4d; then 8mg/kg tds for 6d. The standard course of treatment is 10d. Treatment should not routinely continue beyond this, as severe anaemia can develop. Response to treatment should be guided by clinical improvement and not by NAT testing as the NAT may remain positive for weeks despite clinical improvement.

Supportive care is as for EVD and MVD (➲ Ebola and Marburg virus diseases, p. 746). Optimal management of bleeding is unknown. Patients should be followed up for post-infection sequelae incl. hearing loss.

Hantavirus infections

Hantaviruses are bunyaviruses whose distribution includes Asia, Europe, and N and S America. There are >20 species, not all of which cause infections in humans.

Patients often report encounters with dead or live rodents (usually mice); infection occurs via contact with urine or faces of infected rodents, primarily through aerosol inhalation. Many outbreaks are seasonal, depending on the species of virus and country.

They generally cause two clinical syndromes: haemorrhagic fever with renal syndrome (HFRS), and hantavirus cardiopulmonary syndrome (HCPS). Both have ↑ vascular permeability. The incubation period is ~2wks (range 1–6wks).

Diagnosis

Diagnosis is best confirmed by serology, as viral RNA becomes undetectable by NAT within a few days.

Hantavirus cardiopulmonary syndrome

HCPS is confined to the Americas. It begins with fever, chills, and myalgias (often severe); N&V commonly develop over the next 2–8d. Diarrhoea, headache and marked abdominal pain can occur. Early thrombocytopenia is common, often accompanied by a left-sided granulocyte shift which is a clue to the diagnosis. After the initial phase, vascular leak and hypoalbuminaemia may → pulmonary oedema with cough and respiratory distress and ↑ haematocrit. The next 2–7d → recovery or death due to coagulopathy, haemorrhage (depending on the virus species) and shock.

Treatment

Treatment is supportive. Manage hypotension with inotropes and vasopressors, and cautious IV fluids due to the risk of pulmonary oedema. Mortality is up to 40% even with advanced support.

Haemorrhagic fever with renal syndrome

HFRS occurs mainly in Asia and Europe; cases have occurred in N America. Classically it causes fever, hypotension, bleeding, and renal failure. The clinical course is variable and some patients have mild symptoms. Nausea, vomiting, and abdominal pain are common. Pharyngeal and conjunctival congestion can occur with some viral species.

Treatment

Ribavirin has shown some efficacy. Supportive treatment includes renal replacement therapy, which has been shown to ↓ mortality.

Severe fever and thrombocytopenia

Caused by the severe fever and thrombocytopenia virus, a bunyavirus in central and eastern China, western Japan, South Korea. Transmission is via ticks; livestock are the probable natural reservoir. Human-to-human transmission incl. nosocomial infection may occur through contact with body fluids.

The incubation period is 7–14d. Most patients have fever, myalgia, arthralgia, and headache. Vomiting and diarrhoea is common.

Diagnosis

Diagnosis is by NAT. Laboratory findings include leukopenia, ↓ platelets, hepatitis, and coagulation abnormalities. Mortality is ~15%.

Treatment

Treatment is supportive.

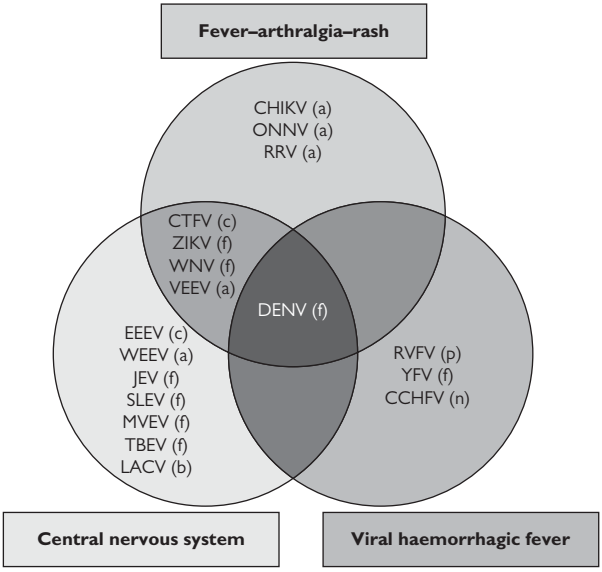

Fig. 17.23 Summary of arbovirus syndromes. (a) alphavirus, (c) coltivirus, (f) flavivirus, (b) bunyavirus, (n) nairovirus and (p) phlebovirus. CCHF, Crimean–Congo haemorrhagic fever; CHIKV, chikungunya; CTFV, Colorado tick fever; DEN, dengue; EEEV, Eastern equine encephalitis; JEV, Japanese encephalitis; LACV, La Crosse virus; MVEV, Murray Valley encephalitis; ONNV, O'nyong'nyong virus; RRV, Ross River fever; RVFV, Rift Valley fever; SLEV, St. Louis encephalitis; TBEV, tick-borne encephalitis; VEEV, Venezuelan encephalitis; WEEV, Western equine encephalitis; WNV, West Nile fever; YFV, yellow fever; ZIKV, Zika virus. Adapted with permission from Solomon T in Beeching N, Gill G, eds., *Lecture notes: tropical medicine* (New York: Wiley; 2014), p. 274.

Zika virus

Zika virus (ZIKV) is a mosquito-borne flavivirus first described in humans in Uganda and Tanzania in 1952. Transmission is mainly by *Aedes aegypti* mosquitoes. Since 2007, transmission/outbreaks have been reported widely in tropical and subtropical regions in Africa, the Americas, Asia, and the Pacific. Transmission also occurs vertically during pregnancy, via sexual contact, blood transfusion, and organ transplantation.

Clinical features

Incubation is 3–14d. Most infections are asymptomatic. Symptoms incl. mild fever, rash, conjunctivitis, myalgia, arthralgia, malaise, and headache for 2–7d. Rarer neurological complications incl. GBS, neuropathy, and myelitis.

Both asymptomatic and symptomatic infection during pregnancy may → congenital Zika syndrome with microcephaly and/or other abnormalities (limb contractures, spasticity, eye abnormalities, and hearing loss), preterm birth, or miscarriage.

Diagnosis

Diagnostic testing is recommended for symptomatic individuals and asymptomatic pregnant women with risk exposure. WHO recommends NATs using blood and/or urine if <7d of illness onset (viremia falls rapidly after 7d). Serology is useful if >7d since symptom onset; antibody cross-reactivity with other flaviviruses may occur.

Management

Care is supportive. Follow latest national guidelines for following up confirmed infection or risk exposure during pregnancy.

Prevention

- Mosquito bite avoidance measures are advised.
- WHO recommends that pregnant women avoid travel to areas with ZIKV transmission, particularly during outbreaks; and that travellers returning from affected areas use barrier contraception for 2mths (women) or 3mths (men) after last possible exposure.
- There is no vaccine available currently.

Japanese encephalitis

Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus first described in Japan in 1871. JEV is endemic in 24 countries in SE Asia and the Western Pacific, where it is the most common cause of viral encephalitis, with ~68,000 cases annually.

JEV mainly affects children, since many adults in endemic countries have natural immunity after childhood infection, but individuals of any age may be affected. JEV is mainly transmitted to humans by *Culex* mosquitoes (e.g. *Culex tritaeniorhynchus*).

Transmission may occur all-year around in tropical regions, but ↑ after the rains due to ↑ mosquito populations. Major outbreaks occur every 2–15yrs.

Clinical symptoms

The incubation period is 4–14d. Most infections are asymptomatic or mild (fever and headache). In children, abdominal pain and vomiting may be the main initial symptoms. ~1 in 250 infections → severe disease characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, and spastic paralysis. Mortality among those with encephalitis is up to 30% and the risk of permanent neurologic or psychiatric sequelae is 30–50%.

Diagnosis

Suspect JE in any individual with encephalitis who lives in, or has travelled to, a JEV endemic area within the previous 14 d. WHO recommends testing for JEV-specific IgM antibody in a CSF or serum, using an IgM-capture ELISA. Testing of a CSF sample gives less false +ve results from previous infection or immunization. IgM antibodies are usually detectable 3–8d after onset and persist for 30–90d, occasionally longer. Positive IgM antibodies may reflect past infection or immunization, and cross-reactivity with other flaviviruses may occur. If positive confirm with neutralizing antibody testing. If negative, repeat on a convalescent sample.

Management

There is no specific treatment besides supportive care.

Prevention

- Effective vaccines are available (➲ Japanese encephalitis vaccines, p. 854). WHO recommends routine immunization in areas of JEV transmission risk.
- JEV is a very low-risk disease for most travellers to endemic countries. Vaccination is therefore only recommended for those spending extensive time in JEV endemic areas, depending on areas visited, activities, season, and other risk factors.
- Mosquito bite prevention measures.
- Vector control.

Dengue virus

Dengue virus (DENV) is a *flavivirus* transmitted from infected humans by *Aedes* mosquitoes, mainly *Ae. aegypti* or *Ae. albopictus*—domestic mosquitoes that breed in human-made containers. These also spread zika and chikungunya viruses and co-infection can occur. The three arboviral diseases produce similar clinical symptoms during the first days of illness, but there are clinical differences (Fig. 17.23) which, together with region and travel history, can help guide diagnosis.

DENV is the most commonly diagnosed arbovirus worldwide. It is common in >100 countries, with ~390 million people infected each year. Transmission is most intense in Southeast Asia. There has also been ↑↑ transmission in the Indian subcontinent, the Americas, and the Western hemisphere in recent years (Fig. 17.24).

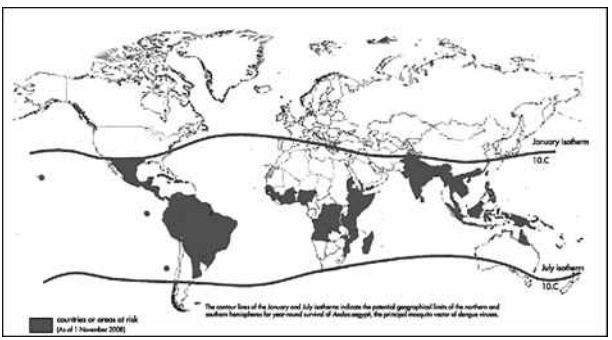

Fig. 17.24 Countries/areas at risk of dengue transmission, 2008 (shaded areas). Lines represent January and July isotherms, which indicate potential geographical limits of northern and southern hemispheres for year-round survival of *Aedes aegypti*, principal mosquito vector of dengue viruses. Adapted from *Dengue: Guidelines for diagnosis, treatment, prevention and control*, p. 3, Figure 1.1 © WHO 2008. All rights reserved.

Transmission

There are four dengue serotypes (DEN-1, DEN-2, DEN-3, DEN-4). 'Asian' genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections.

Recovery from infection → lifelong immunity against that serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes ↑ the risk of developing severe dengue, due to antibody-dependent enhancement.

Transmission is mainly human–vector–human → urban outbreaks. Transmission may also occur during pregnancy, and via breast milk, blood transfusion, organ transplant, and needlestick injury.

Clinical features

The incubation period is 3–15d. Infection can be asymptomatic, or cause clinical dengue fever (DF) which can progress to severe dengue. WHO recommend distinguishing DF without warning signs, DF with warning signs and severe DF (Fig. 17.25). The early clinical features are indistinguishable between severe and non-severe dengue cases. Careful monitoring for warning signs and other clinical parameters is crucial to recognize progression to severe disease.

Suspect DF if high fever accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, and headache. Anorexia and N&V are common. Pharyngitis and conjunctival injection may occur.

A probable case is defined by WHO as fever in a patient that lives in or has travelled to dengue endemic area within the previous 15d, accompanied by two of the following: nausea, vomiting, rash, aches and pains, a positive tourniquet test (Box 17.19), leukopenia, or any warning sign of severe dengue (Fig. 17.25).

Most cases recover after 2–7d; a small % progress to severe disease, mostly characterized by plasma leakage +/− haemorrhage (see later in topic). DENV can occasionally → encephalitis.

Mortality from severe dengue is high without treatment, but may be reduced to 1–5% with appropriate supportive care.

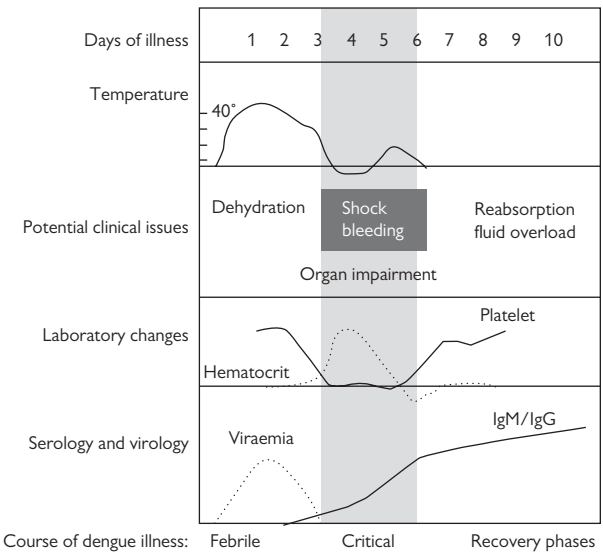

Fig. 17.25 The course of dengue illness. Reproduced with permission from Yip, WCL, *Medical Progress*, 7 (13), pp. 201–9, Dengue haemorrhagic fever: Current approaches to management, 1980.

Box 17.19 Tourniquet test

The Tourniquet test is a measure of capillary fragility.

- Inflate a BP cuff to half way between the patient's systolic and diastolic BP for 5min.
- Then deflate the cuff and wait for 2min.
- Count the petechiae in the antecubital fossa.
- The test is positive if there are ≥10 petechiae in a 2.5cm² area.

The tourniquet test has variable sensitivity and specificity. In dengue, it is most sensitive around the time the fever ceases. It is less sensitive in patients with shock. Using a cut off of ≥20 petechiae/2.5cm² ↑ specificity but ↓ sensitivity (http://www.cdc.gov/dengue/training/cme/ccm/Tourniquet%20Test_F.pdf).

Warning signs of severe dengue occur 3–7d after symptom onset, usually around the time the fever ceases. Warning signs incl. abdominal pain or tenderness, persistent vomiting, mucosal bleeding, lethargy, restlessness, liver enlargement >2cm, fluid accumulation, and ↑ haematocrit (2° to ↑ capillary permeability) accompanied by rapidly ↓ platelets. *Warning signs are a medical emergency requiring strict observation and medical intervention*. Some patients → critical phase of plasma leakage while still febrile.

Severe dengue is defined by one or more of the following:

- Plasma leakage that may → shock and/or fluid accumulation, with or without respiratory distress.
- Severe bleeding.
- Severe organ impairment (Fig. 17.26).

As vascular permeability progresses, hypovolaemia worsens → shock.

Laboratory diagnosis

Laboratory diagnosis in symptomatic patients is by serum NAT or NS1 antigen test and IgM antibody during the 1st 7d of illness. NS1 tests detect the non-structural protein NS1 of DENV. Rapid diagnostic tests are available. Performing both NAT/NS1 and IgM antibody tests provides optimum sensitivity, and usually allows diagnosis with a single sample. If both tests are negative and the diagnosis is still suspected, test for IgM antibodies on a convalescent sample taken >7d after illness onset. IgM antibodies are usually present for ≥3mths; cross-reactivity with other *flaviviruses* may occur.

Management

Management is supportive. Avoid NSAIDs and aspirin due to risk of bleeding. Severe dengue requires urgent medical care with prompt restoration of circulating volume. The vascular leak typically resolves within 24–48h, and careful monitoring is required to avoid fluid overload. Pulmonary oedema 2° to fluid overload can contribute to mortality. For more information see WHO guideline: https://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf.

Box 17.20 Prevention

- Vector control measures.
- Bite prevention measures. Those with acute dengue should protect themselves from mosquito bites for 12d post symptom onset to prevent human–vector–human transmission to others.
- The first dengue vaccine, Dengvaxia® (CYD-TDV, Sanofi Pasteur) was licensed in 2015 and approved for 9–45yr-olds in endemic areas in 20 countries. The live attenuated vaccine is efficacious and safe in those who have had a previous DENV infection, but carries ↑ risk of severe dengue in those who experience their first natural dengue infection after vaccination. WHO currently recommend prevaccination screening, reserving vaccination for people with confirmed previous dengue infection in endemic areas. The vaccine is not recommended for use in travellers to endemic areas. (For updates, see: http://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue.)

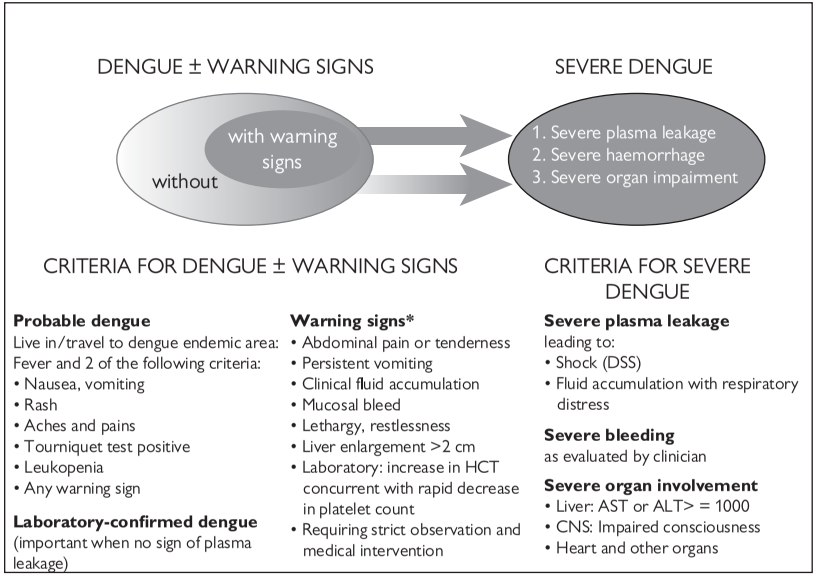

Fig. 17.26 WHO suggested dengue case definition and levels of severity. Reproduced with permission from *Dengue: Guidelines for diagnosis, treatment, prevention and control*, p. 11, Figure 1.4 © WHO 2008. All rights reserved.

Yellow fever

Yellow fever (YF) is caused by a mosquito-borne *flavivirus*. 'Yellow' refers to jaundice, which is not always present. There are ~200,000 YF cases → ~30,000 deaths/yr worldwide, most in sub-Saharan Africa, with far fewer in Central and S America (Fig. 17.27). Although YF has never been reported in Asia, the region is potentially at risk because conditions exist for transmission. Direct human-to-human transmission has not been reported.

Transmission

Jungle (sylvatic) YF → asymptomatic infection of non-human primates that maintain the reservoir of infection in tropical rain forest. Sporadic infection in humans occurs when they are bitten by infected mosquitoes in these forests. Localized outbreaks may occur in humid savannah regions of Africa where mosquitoes infect both monkeys and humans (intermediate/savannah YF).

If a viraemic person enters an urban environment, *Aedes aegypti* mosquitoes can spread the virus from human to human with the potential for explosive urban epidemics in unvaccinated populations. The urban cycle is rare in S America, where most infections are in persons living or working in tropical rainforest areas (Fig. 17.28).

Clinical features

Infection may be subclinical. The incubation period is 3–6d. Characteristic features are fever, chills, headache, backache, nausea, vomiting, myalgia, and conjunctival injection. This 'acute phase' usually resolves spontaneously within 3–4d. However, in ~15% of patients, a 'toxic phase' develops within 24h of the initial remission of fever, with jaundice, abdominal pain, diarrhoea, and renal failure. Thrombocytopenia and coagulopathy can → frank bleeding from gums, nose, eyes, and GI tract. There may be relative bradycardia (Faget's sign). Up to 50% of cases with severe disease will die within 2wks.

Diagnosis

Diagnosis is usually made by detection of IgM by capture ELISA or by detection of virus in blood by NAT in the first few days of illness. Virus can be detected in postmortem liver tissue.

Management

Treatment is supportive. Organ support is appropriate if available. Blood product support including FFP should be used for bleeding.

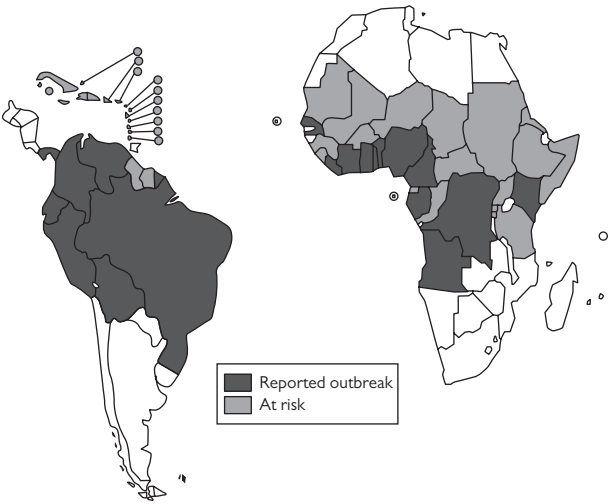

Fig. 17.27 Countries at risk from YF (shaded) and reported cases from 1985–2004 (dark shading). Adapted with permission from the WHO dengue guidelines for diagnosis, treatment, prevention and control (2009).

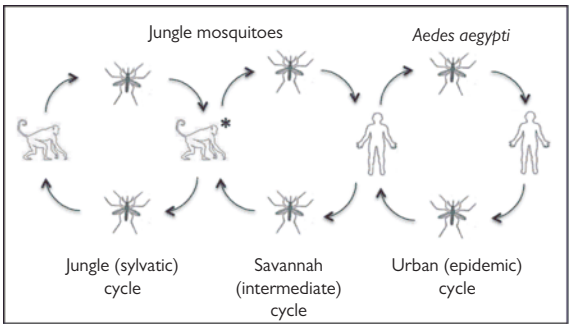

Fig. 17.28 Transmission cycle of YF virus in Africa (savannah YF does not occur in South America, and the urban cycle is rare).

*Humans entering jungle environments can be incidentally infected at this point.

Public health note

Prevention

- Immunization is the most effective preventive strategy. YF vaccine is generally safe, affordable, and highly effective, though there is a small risk of severe adverse events, particularly in the elderly (➲ Yellow fever vaccine, p. 854).
- Vector control can be effective but is difficult to sustain.

Management of a yellow fever (urban) outbreak

- Notify WHO of any confirmed YF case (required under international health regulations).
- Implement infection control measures.
- Mass immunization: if resources limited, target children aged 9mths–14yrs.
- Vector control focused on *Aedes* breeding sites. Refill and cover domestic water containers. Remove receptacles that collect water, e.g. discarded tires, tins, and jars.
- In a large urban outbreak, consider widespread insecticide spraying.
- Local surveillance: collect specimens for laboratory diagnosis from any new suspected cases (postmortem if necessary).

Longer-term prevention measures

- Include YF vaccine in routine childhood EPI schedule (can give at 9mths with measles vaccine).
- Provide health education messages: domestic water containers should be covered with a lid or screen; waste items that can collect standing water should be buried or disposed of in a safe manner.

West Nile virus

West Nile virus (WNV) is a flavivirus first identified in Africa in 1937, and now present in Africa, Europe, the Middle East, the Americas, Australia, and W Asia. Transmission by *Culex* mosquitoes maintains the virus in birds (the main reservoir). Humans are accidental hosts usually infected by *C. pipiens* mosquitoes. Transmission may also occur via blood transfusion, organ donation, and vertically during pregnancy and via breast milk.

Clinical features

The incubation period is 3–14d. ~80% of infections are asymptomatic. Symptoms of West Nile fever incl. headache, myalgia, joint pains, vomiting, diarrhoea, rash. Most patients make a complete recovery, but fatigue can last for months. <1% develop neuro-invasive disease with encephalitis, meningitis, or myelitis. Symptoms of severe disease include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness and paralysis. Risk groups for severe disease are people >50yrs or immunocompromised. Mortality is 3–15% in severe disease, highest in those >75yrs old.

Diagnosis

NATs for viral RNA can be performed on serum, CSF, or tissue specimens collected early in the illness; a −ve result does not rule out WNV infection. WNV-specific IgM antibodies are usually detectable by 8d after illness onset, and persist for 30–90d (occasionally longer); positive IgM antibodies may reflect a past infection, and cross reactivity with other flaviviruses may occur.

Management

Management is supportive. Prolonged ventilatory support may be required for neuro-invasive disease. Monitor closely for signs of ↑ ICP.

Prevention

- Vector control.
- Prevent risk of transmission through blood transfusions—follow blood donation restriction guidelines during outbreaks/exposure.
- There is no licensed vaccine for humans.

Kyasanur Forest disease

Kyasanur Forest disease virus is a tick-borne flavivirus endemic in S India. Fever and headache are common. It can → bleeding. Treatment is supportive. A vaccine exists.

Chikungunya

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus, mainly transmitted to human via *Aedes aegypti* and *Ae. albopictus* mosquitoes. The name 'chikungunya' derives from a word in the Kimakonde language, meaning 'to become contorted', and describes the stooped appearance of sufferers with arthralgia. CHIKV has a wide geographical range including sub-Saharan Africa, India, Indian Ocean islands and much of SE Asia. In recent decades the mosquito vector has spread and was reported in Europe in 2007, where localized travel-imported outbreaks have since been reported during the summer season, through human–vector–human transmission.

Clinical features

The illness begins abruptly 3–12d after the bite of an infected mosquito. The most common symptoms are fever and polyarthralgia, which usually symmetrically involve the hands and feet. Other symptoms resemble DF, incl. headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, and a maculopapular rash. Laboratory findings incl. lymphopenia, ↓ platelets, ↑ creatinine, and ↑ hepatic transaminases.

Documented complications incl. myocarditis, hepatitis, and haemorrhagic, ocular, and neurological manifestations. Confirmed cases of meningoencephalitis have occasionally been reported in neonates and the elderly.

Mortality is low (0.02%), but recurrent, symmetric, often debilitating joint pain can persist for months or years in up to 30–40% of cases.

Diagnosis

Clinical symptoms and travel history suggest the diagnosis. Often misdiagnosed as DF due to similar presentation. Diagnosis may be confirmed by NAT for CHIKV RNA (present in serum up to 8d after symptom onset) and/or serology for anti-CHIKV IgM (normally present from the end of the first week, peaks 3–5wks after the onset of illness and persist for about 2mths). Testing samples taken in the 1st week of illness with both NAT and serology maximizes sensitivity.

Management

Treatment is symptomatic. Avoid aspirin and other NSAIDs unless dengue infection excluded.

Prevention

- Vector control.
- Mosquito bite prevention measures.
- Confirmed cases should protect themselves from mosquito bites to reduce risk of transmission (human–vector–human) to others.
- There is no vaccine available.

Ross River fever

Caused by Ross River virus (RRV), an *alphavirus* endemic in Australia and islands of the western South Pacific. Ross River fever frequently occurs in tropical coastal regions with salt marsh habitats, the natural habitat for the main mosquito vector species. Infection is most common following the rainy season and the flooding of salt marshes. However, cases can occur in more arid regions after rains, when desiccation-resistant mosquito eggs, within which the virus persists, hatch.

Incubation is usually 3–9d (up to 21d). Subclinical infection is common. Common symptoms are fever, myalgia; a symmetrical polyarthritis involving small and large joints; and a maculopapular rash. Arthralgia can persist for months. Diagnosis is usually by serology for RRV-specific IgM. Treatment is with NSAIDs.

O'nyong'nyong

O'nyong'nyong (ONNV) is a mosquito-borne alphavirus related to CHIKV that is found in Central and E Africa and transmitted by anopheline mosquitoes. The clinical picture resembles CHIKV infection, with self-limiting fever, headache, rash, and joint pain. In contrast to CHIKV, ONNV is reported to cause lymphadenopathy more often and affected joints do not show effusions. It is non-fatal.

Mental health

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Introduction

Mental illnesses account for >10% of the global burden of disease; this proportion is likely to ↑ as populations age and other health problems are controlled. Common mental disorders (depression, anxiety), alcohol use disorders, psychoses (schizophrenia, bipolar disorder), and intellectual disabilities (IDs), are the leading psychiatric causes of disability.

In most communities, mental illnesses are equated with psychoses. Depression, anxiety, and substance abuse, which account for most mental morbidity, are seen as social problems, with physical symptoms being the typical clinical presentations. Mental illnesses are ↑ in people with physical illnesses, e.g. diabetes or HIV/AIDS, and may complicate the treatment of physical disorders (e.g. mothers with depression are more likely to have LBW babies and malnourished infants). When people with HIV/AIDS have a mental disorder, this may interfere with their HIV care. Mental disorders are associated with ↑ mortality, through suicide, physical disease (e.g. liver damage from alcohol abuse), and worsening of outcome of comorbid physical health problems (see Box 18.1 for terminology).

Most mental disorders can be treated effectively using cheap and relatively simple interventions, delivered by primary or community HCWs. Yet most mental disorders are not recognized by HCWs, and treated inappropriately or not treated at all. ↓ knowledge and skills, not having enough time, and the stigma attached to mental disorders (especially psychoses) are major obstacles.

Box 18.1 Terminology: making sense of mental illness

Terms used for mental disorders are heavily influenced by language, e.g. if very few patients complain of 'depression', then the term 'depression' has limited meaning for doctors or patients. However, in all languages, one can find locally meaningful words to describe emotional and behavioural states that indicate a mental disorder. Use the following descriptions to find out what the most appropriate words are to improve communications with your patients and other health workers.

- A condition where the person thinks too much, cannot sleep, and is tired all the time (*probable diagnosis*: common mental disorders = anxiety and/or depression).
- A condition where the person gets very scared or frightened for no reason (*probable diagnosis*: panic disorder or PTSD).
- A condition where the person behaves in a strange way, says strange things, holds strange beliefs, or hears things that are not really there (*probable diagnosis*: severe mental disorders = psychoses).
- A health problem where the person drinks too much alcohol or uses drugs (*probable diagnosis*: alcohol or drug use disorder).
- A condition in which a child does not learn as well as others in school (*probable diagnosis*: ID).

Suicide and deliberate self-harm

Deliberate self-harm may take many forms, e.g. deliberate overdosing with medication, self-poisoning with pesticides, self-cutting, hanging, or burning. The motivations can vary widely and several may play a role simultaneously. There are large variations between countries in the incidence and methods used depending on socio-cultural and economic conditions. In most cases, the patient likely has a mental illness, typically depression or alcohol use, or a chronic and debilitating physical illness (e.g. HIV/AIDS). Major risk factors incl. social factors (esp. financial difficulties and violence) and, in young people, educational pressures and conflict with parents/partners. The lethality of suicide attempts varies considerably between the sexes and populations, both due to method used, and availability and access to emergency medical care.

Management of self-harm

- First treat medical consequences of suicide attempt (➲ Acute pesticide poisoning, p. 814).
- Try to see person quickly, or offer a place to wait that minimizes distress.
- Decide whether there is an imminent risk of suicide (Box 18.2).
- Remove dangerous/sharp objects and ensure constant monitoring to maintain safety.
- Suicide is a sensitive and personal matter. Talk to the patient in private. Give the patient enough time to feel comfortable and share their reasons frankly.
- Do not make judgements about the patient's character; do not make reassuring statements without fully understanding the patient's situation → this may make the patient feel even more hopeless.
- Talk to family or friends for their version of the patient's recent life situation and health.
- Assess mental state (look for common mental disorders, alcohol or drug dependency, and psychotic disorders) and offer appropriate treatment.
- Optimize management of any painful or debilitating conditions.
- Help patient address the problems. May be psychological, social (e.g. financial problems, relationship difficulties), or physical (e.g. chronic illness); see ➲ Box 18.5, p. 776.
- Explore reasons to live and ways to stay alive.
- Enlist the help of others (e.g. relatives or friends, social workers, counsellors), with the consent of the patient, to provide close monitoring while at high risk of suicide and provide social support. Support caregivers too.
- If prescribing, give least dangerous medications and only small amounts of medication at any one time.
- If high risk of suicide, consult a specialist mental health worker.
- Ensure you give a follow-up appointment <1wk.

Box 18.2 Assessment of suicide risk

Consider suicide risk in all patients with mental illnesses. Patients are rarely embarrassed, and often very relieved, to be asked tactfully about suicide. Asking about suicidal thoughts does not ↑ risk for suicide. Simple questions you might ask are:

- 'Feeling as you've described recently, have you felt that life was a struggle? Have you felt as if there was no point in living anymore?'
- 'Patients with similar difficulties to you sometimes tell me they feel like ending their life. Have you felt like that?'

Is there imminent risk of suicide?

- Current thoughts or plan to commit suicide *or*
- History of suicidal thoughts/plans in last month or act of self-harm in past year in a person who is now extremely agitated, violent, distressed, or uncommunicative.

What is the future risk of suicide?

- *Intention of act*: what was their motivation? Ask about associated actions and thoughts; go through what led up to act and afterwards. Was there planning/preparation?
- *Method chosen*: how lethal or dangerous was the method chosen? Why did they choose this method, and did they consider alternatives? Did they make any 'final acts' (e.g. writing a suicide note)? Did they take precautions to avoid discovery?
- *What did the act represent*: a wish to die/for help/something else? Did they seek help or tell anyone? Was medical attention willingly sought or were they coerced?
- *Precipitation*: what problems led to the act? Are these likely to recur or persist? What can be done about them?
- *Resources*: what resources are available (self/friends/family/community/health services)? Is the patient isolated? How can this be addressed?
- *Present feelings and intentions*: do they regret or feel guilty about the act or being discovered? Have they changed how they feel? If they go home, will they cope? What do they want now: to die or get help? Will they accept treatment or help?
- *Mental state*: is the patient severely depressed or psychotic? Do they feel hopeless? Are they agitated, violent, distressed, or uncommunicative?
- *Protective factors*: do they have hope for future improvement? Do they have supportive children/partner/family/friends or strong convictions or religious beliefs that would prevent them from committing suicide? Any felt reason to live?
- *Personal history*: previous attempts, chronic pain or illness, social isolation, unemployment, older age (all ↑ risk of eventual suicide).

Acute behavioural disturbance

In most cases, persons with mental illness are not violent, and, indeed, are more likely to be victims than perpetrators of violence. The risk of disturbed behaviour (incl. violence) can be ↑ in persons with untreated psychosis, esp. when accompanied by substance misuse. In acutely disturbed behaviour, it is critically important to exclude medical or traumatic causes that can cause delirium.

When seeing a patient in a state of acute disturbance

- *Safety first*: do not see patient alone. Ensure clear path to the exit (for both patient and yourself).
- *Try to de-escalate the situation*: respect patient's rights and dignity, irrespective of how disturbed they may be. Avoid confrontation or argument. Where it is necessary to intervene, do it calmly and firmly. One member of the team leads the effort, takes control of the situation, and gives clear instructions.
- If patient brought to you in restraint, don't rush to release restraint before patient is calm enough (verbal de-escalation or medication)
- *Look for evidence of severe medical illness*: ask for any history of medical illness or drug use.
- If possible, check pulse, BP, temperature, and blood glucose and look for any indicators of acute confusion or delirium (➲ Acute confusional state and delirium, p. 384) or drug intoxication (➲ Disorders due to substance abuse, p. 784). Treat underlying cause.
- If cause of behavioural disturbance not immediately reversible, and person is a potential danger to themselves or others, administer sedative medications (Box 18.3).
- Acutely disturbed patients, esp. those with acute manic episodes, may need to be admitted to hospital and require intensive nursing. If this is not available, try to arrange a safe environment with adequate supervision (e.g. from a family member or nurse).

Box 18.3 Rapid tranquillization of the acutely disturbed patient

Start by offering oral medication: if already taking an antipsychotic medication, offer diazepam 10mg oral (avoid benzodiazepines in delirium) or promethazine 50mg oral. If not already taking antipsychotic medication, then consider chlorpromazine 25–50mg oral or risperidone 1–2mg oral, or haloperidol 1.5–5mg oral (use haloperidol with caution if history of IHD; avoid if ↑ QT interval).

If refusing oral medication

- Give lorazepam 1–2mg IM (if available) or promethazine 50mg IM. Alternatively, diazepam 5–10mg IV can be given. Avoid IM diazepam as absorption is erratic. Consider haloperidol 5mg IM as a last resort (acute dystonia is common).
- If insufficient improvement with either oral or IM sedation, repeat after 30–60min, up to 2×.
- IV diazepam 5–10mg can be used as an alternative if it can be administered safely. Give over at least 5 min. Wait 5–10min for a response and repeat up to 3×.
- Monitor temperature, pulse, BP, and RR/effort several times in the first hour, and regularly thereafter, until the patient is walking around again.
- If RR drops <10 breaths/min after administration of diazepam or lorazepam, give flumazenil to reverse benzodiazepine.

Common mental disorders

Common mental disorders are depressive and anxiety disorders, most often seen in 1° care. Although psychiatric classifications deal with depressive disorders and anxiety disorders separately, many patients have symptoms of both, both have similar risk factors, and both respond to similar treatments. The term 'common mental disorders' is often used when describing the practical, clinical approach to these disorders.

Common mental disorders are among the most important causes of morbidity in 1° care and are the leading mental health cause of disability worldwide. However, these disorders are often missed, because few patients complain of psychological symptoms. Moreover, there is a tendency to prescribe benzodiazepines or placebo treatments (e.g. vitamins) when specific and efficacious treatments exist: antidepressants and brief psychological treatment.

Clinical features

Although the terms 'depression' and 'anxiety' imply a sad mood or feeling fearful, few patients complain of emotional or cognitive (thinking) symptoms. Patients classically have physical complaints which are non-specific, multiple, and referable to multiple body parts, and are usually medically unexplained (Box 18.4). On inquiry you can readily elicit emotional and cognitive symptoms. Sometimes, relatives may misinterpret these symptoms as signs of laziness. Physical symptoms with no medical cause can also occur in the absence of depression or anxiety, understood to be a subconscious way of coping with psychosocial stressors (so-called somatization). Certain patients would experience loss of neuromuscular functions which is not in keeping with known anatomy and physiology (e.g. glove anaesthesia, sudden onset and offset of body weakness). In some individuals, irritability or severe symptoms of anxiety may dominate (e.g. panic attacks and phobias; see later in this topic). Panic attacks may present as an emergency (e.g. with acute chest pain).

Diagnosis

Anxiety and depression are normal human experiences in appropriate situations, e.g. to feel miserable when a relative dies, or a student before an examination will feel anxious and tense. Depression/anxiety is diagnosed as an illness if a patient experiences symptoms nearly every day and most time of the day, lasting >2wks, interfering with daily life. The focus is on the presence of emotional symptoms with little regard about what might have caused the feeling states (e.g. losing an employment status). Suspect a common mental disorder when physical complaints do not fit into the pattern of common physical illnesses. Remember that common mental disorders are ↑ frequent in persons with chronic physical health problems; always assess depression and anxiety in such patients. Also at ↑ risk are those using drugs or alcohol, smokers, women, and people facing severe economic or social difficulties.

In all patients, inquire about drug and alcohol use (alcohol/drugs may be used to self-treat anxiety, or anxiety and depression may be the consequence of dependence). Medications can cause depression and/or anxiety, such as steroids, β-blockers, ART (e.g. efavirenz and nevirapine),

oestrogens, anticonvulsants, statins, ciprofloxacin, calcium channel blockers and others. Ask about history of head injury, as this may → depressive and anxiety symptoms. Rarely, anxiety and depression may be the presenting symptoms of another medical disorder (e.g. hypothyroidism, epilepsy).

Box 18.4 Clinical features

Depression

Presenting complaints

- Tiredness, fatigue, and weakness.
- Vague aches and pains all over the body.
- Crawling or burning sensations.
- Disturbed sleep (usually ↓, but occasionally ↑ sleep).
- ↓ appetite (sometimes ↑ appetite).

Complaints on inquiry

- Feeling sad and miserable.
- Feeling a loss of interest in life, social interactions, work, etc.
- Feeling irritable.
- Feeling guilty.
- Feeling hopeless about the future.
- Difficulty making decisions.
- 'Thinking too much.'
- Thoughts that one is not as good as others (low self-esteem).
- Thoughts that it would be better if one was not alive.
- Suicidal ideas and plans.
- Difficulty in concentrating.

Anxiety

Presenting complaints

- Palpitations.
- A feeling of suffocation.
- Chest pain.
- Dizziness.
- Trembling, shaking all over.
- Headaches.
- Pins and needles (or sensation of ants crawling) on limbs or face.
- Poor sleep.
- Nausea, non-specific abdominal complaints.

Complaints on inquiry

- Feeling as if something terrible is going to happen.
- Feeling scared.
- Worrying too much about one's problems or one's health.
- Thoughts that one is going to die, lose control, or go mad.

Common management principles

- Use a stepped care approach, i.e. give advice to all patients and reserve medication or psychological treatment for those who do not recover or are moderate/severely depressed (e.g. actively suicidal).
- Rule out medical disorders or medication side effects.
- After confirming diagnosis, assess suicide risk (➲ Box 18.2, p. 770). There is no evidence that asking about suicide 'puts ideas into their head'.
- Reassure patient and relatives that just because there are no physical signs or diagnoses, this does not mean that patient is 'making it up'.
- Let patient know that s/he is having an illness despite negative laboratory tests and the condition is treatable.
- *Counter stigma*: a common problem that can happen to anybody.
- *Instil hope*: explain that effective treatment is possible.
- Identify and ↓ substances that predispose to depression and/or anxiety (e.g. cigarettes, chewing khat (*Catha edulis*), alcohol).
- Identify and discuss ways of ↓ work pressures, disabilities, or conflict at home. Speak with the spouse or relatives.
- Encourage the patient to stop concentrating on –ve ideas or acting on them (e.g. leaving work).
- *Avoid the 'pull yourself together' or 'there is nothing wrong with you' approach*: patients are caught up in guilt and feelings of failure, and do not need to be blamed for their symptoms.
- Recommend a regular sleep cycle and physical activity.
- Encourage abstinence from any substance use (e.g. alcohol).
- Behavioural activation and reactivation of previous social networks and activities can be simple but effective ways to improve mood (Box 18.5).
- A problem-solving approach can also help (Box 18.5).
- Identify supportive family members and involve them in the patient's care.
- Refer the person to appropriate agencies for social problems (e.g. economic difficulties or intimate partner violence).
- Medication is useful for moderate and severe depressive episodes with 70–80% of patients showing an improvement (Box 18.6).
- Offer regular follow-up.
- *If patient does not respond*: review diagnosis, ensure treatment adherence, check for comorbid alcohol or substance misuse, and consider ↑ drug dose or changing to an alternative class of drug.

When medically unexplained symptoms are the main complaint

- Only carry out indicated medical investigations.
- Avoid placebo treatments.
- Acknowledge the patient's symptoms and suffering are real.
- Communicate test results clearly. Reassure that no dangerous disease has been identified, but that it is important to treat distressing symptoms.
- Identify psychosocial stressors and ask about links to physical symptoms.
- Explain how stress can ↑ health problems, incl. physical complaints, e.g. physical sensations experienced when a person is very scared.
- Explain that stress can make pain worse and needs to be treated too.
- Emphasize the importance of a gradual return to normal activities.

- Advise the person to consult you first if symptoms worsen or new symptoms appear, so that they do not waste money on ineffective treatments.
- Arrange regular follow-up.

Box 18.5 Psychosocial interventions for common mental disorders

Relaxation training

These techniques need to be practised, ideally daily, to develop the ability to relax before and during stressful situations.

- *Progressive muscle relaxation*: in a quiet environment, close eyes, tensing then relaxing muscles, starting from feet, then legs, then thighs, etc., up to the head. Concentrate on the relaxed feelings.
- *Controlled breathing*: close eyes; breathe in and out to a slow count of 4 or 5. Continue for 5min. Patient can say in his/her mind a religious or calming word while exhaling.
- *Imagery*: visualize a scene that is calm, safe, and relaxing. Concentrate on the details—smells, sounds, and feel of the place.
- *Distraction*: focus attention away from anxious thoughts and sensations and on to something relaxing and absorbing.

Problem-solving

Common mental disorders are often consequence of practical problems the patient is facing in their daily lives. Unfortunately, disorders ↓ ability of patient to take steps necessary to overcome their problems. Problem-solving aims to empower the patient to regain control over their lives.

- Explain treatment.
- Define problems (what are different problems faced by patient).
- Summarize problems (how are these problems related to patient's symptoms).
- Select one problem and choose goals (why should patient overcome problem).
- Define solutions (small, defined actions to be taken to overcome problem).
- Review the outcome of the actions taken at follow-up: did it make the problem less; did it help improve the patient's mood, what were the barriers experienced, and how can they be addressed.

Behavioural activation

Aim of this psychological treatment is to ↑ exposure to potentially pleasurable activities which the patient may have stopped due to depression, e.g. playing with grandchildren, meeting friends. Identify these previously enjoyed activities. Set an achievable goal (e.g. meet up with friend twice a week), encourage perseverance even when not immediately enjoyable, and build up from there.

Reactivating social networks

Social withdrawal → loss of social support can make common mental disorders worse and interfere with recovery. Identify previous social networks and activities and encourage person to re-engage with these.

Specific presentations

Recurrent depression

Some patients have repeated episodes of depression. Consider long-term follow-up (e.g. monthly) to discuss personal and social issues, and continue antidepressants for 2yrs or more. In addition to an antidepressant, consider a long-term mood-stabilizing medication (e.g. lithium).

Phobic disorder

A phobia is a fear of a specific situation that is out of proportion to the objective risks, beyond voluntary control, and not responsive to reasoning. It results in avoidance of situations in which the trigger might occur (e.g. crowds, open spaces, travelling, social events). Patients may become confined to their house. Phobias can be managed by relaxation training techniques to help them to 'face their fear' (Box 18.5). Use graded exposure (e.g. to feared situation such as crowds) to ↓ avoidance and escape the cycle of reinforcement. Antidepressants may also be effective.

Panic disorder

Panic disorder is characterized by recurrent, frequent, unexpected panic attacks in which the patient experiences severe, acute anxiety accompanied by chest pain, breathlessness, or dizziness that are typically the result of hyperventilation. Panic attacks are best managed using relaxation training techniques in combination with preventing reinforcement of the anxiety through avoidance (e.g. of going out) or escape (e.g. running out of the shop when anxiety symptoms appear). Antidepressants are also effective and benzodiazepines can be used for short-term relief.

Obsessive–compulsive disorder

Obsessional thoughts are recurrent thoughts, ideas, or images that are distressing to the patient who makes efforts (often unsuccessful) to get rid of them (e.g. thoughts of being dirty or blasphemous or ugly). Compulsions are behaviours that are repeated (e.g. cleaning or counting rituals), even though patient recognizes that this is irrational, but is unable to resist urge to carry them out. Management involves psychological treatments (e.g. cognitive behavioural techniques) or antidepressants (e.g. fluoxetine, clomipramine, usually requiring treatment at high end of the therapeutic range, and for a longer period than for depression).

Box 18.6 Medicines for common mental disorders

Antidepressants

There are two major classes:

- *Tricyclic antidepressants (TCAs)*: e.g. imipramine or amitriptyline, initially 50mg oral od at night, ↑ by 25–50mg/wk. Min. effective dose is 75mg; max. daily dose 200mg, given as a single dose at night time.
- *Selective serotonin reuptake inhibitors (SSRIs)*: e.g. fluoxetine, initially 20mg oral od (also min. effective dose), max. daily dose 60mg given as a single dose in the morning with or after food.

Choice of antidepressant is influenced by:

- *Toxicity*: if risk of overdose is high, avoid TCAs.
- *Side effect profile*: avoid TCAs in patients with heart disease.
- *Age*: avoid TCAs in adolescents and the elderly; in adolescents, fluoxetine is the antidepressant of choice, but should be used only if psychosocial treatments are not feasible or ineffective.
- Symptoms: consider more sedative medication (e.g. amitriptyline, imipramine) in anxious or sleep-deprived patients.

Regimen

- Explain that antidepressants are not addictive.
- Build up to the minimum effective dose within the 1st week.
- Use lower doses if patient is adolescent, elderly, or medically ill.
- Explain side effects usually fade after 2–3wks and that max. benefit builds up over 3–6wks, provided medication taken daily.
- Regularly review side effects, adherence, and suicidal ideation.
- As long as medication can be tolerated and is at a therapeutic dose, do not ↑ the dose or change class until there has been a proper 'therapeutic trial' (6wks).
- Do not prescribe two antidepressants at same time, except briefly if swapping from TCA to SSRI (but not from SSRI to TCA).
- In patients with bipolar disorder, antidepressants should only be prescribed in combination with a mood stabilizer (or antipsychotic if a mood stabilizer is not available).
- If psychotic features present, outcome better if antipsychotic medication prescribed (➲ Antipsychotic drugs for severe mental disorders, p. 781) in addition to antidepressant.
- Once improved continue antidepressant for at >6mths (and preferably up to 1yr) to minimize risk of relapse.

Withdraw gradually to avoid discontinuation syndromes.

Anxiolytic medications

- When using antidepressants to treat anxiety, use a lower starting dose and explain that anxiety may get worse temporarily.
- Benzodiazepines (e.g. diazepam 2mg oral tds, ↑ as necessary to 5–10mg tds) should only be used for short-term (<2wks) relief of severe and disabling anxiety symptoms. Dependence and reinforcement of anxiety may occur with longer use. See ➲ Management of specific withdrawal states, p. 787 for advice on withdrawing benzodiazepines in cases of dependency.

Severe mental disorders (psychoses)

This group of disorders consists of schizophrenia, bipolar disorder (manic-depressive disorder), and other psychotic disorders (e.g. delusional disorder, brief psychotic episode, schizoaffective disorder). Psychoses are relatively rare and characterized by marked behavioural problems, abnormal experiences, gross deviation to societal norms (e.g. disrobing or masturbating in public), and strange or unusual thinking. Most patients in psychiatric hospitals have psychoses. Most cultures equate mental disorders with the psychoses but it is critically important to differentiate severe mental disorders from organic psychosis or delirium (Box 18.7). In organic psychosis, the psychotic symptoms are the result of an underlining physical illness (e.g. brain lesion or systemic illness). Rule out an organic illness that may be the cause of the psychotic manifestation, as it is usually life-threatening.

Clinical features of psychoses

- *Delusions*: false beliefs, not in keeping with the patient's cultural or educational background which are held with a strong conviction and the patient cannot be persuaded to think otherwise despite evidence, e.g. body or mind are under external control, or that thoughts are being inserted, withdrawn, or broadcast from their mind, or persecutory or grandiose delusions, or other very bizarre beliefs.
- *Thought form disorder*: inability to communicate coherently, with thinking and speech becoming illogical and irrelevant.
- *Hallucinations*: perception in the absence of an external stimulus, commonly auditory, e.g. voices speaking directly to the patient, giving a running commentary or orders, experience of their thoughts being spoken aloud, or other persistent auditory, visual, olfactory, or somatic hallucinations. Patient can be observed to be talking and laughing alone when responding to the hallucination.
- *Disturbed behaviour*: both aggressive or agitated; withdrawn or apathetic behaviour may be seen.
- *Indifference* to the environment.
- *Insight* (awareness of being ill and needing treatment) is often seriously ↓.

Distinguishing bipolar disorder and other psychoses in a patient with psychotic symptoms

- *Affective/mood symptoms*: if there are marked depressive or manic features, most likely diagnosis is psychotic depression or bipolar disorder.
- *Chronicity*: if symptoms have been continually evident for >6mths, likely diagnosis is schizophrenia.
- *Episodic course*: with periods of relatively normal health in between, is more typical of bipolar disorder.
- *Presence of a trigger*: although any psychoses may be precipitated by a trigger, these are the hallmark of acute or brief psychoses.

Schizophrenia

A severe mental disorder that usually begins <30yrs of age. Apart from the usual symptoms of psychoses, patients may also show catatonic behaviour (stupor, mutism, posturing), –ve symptoms (unexplained apathy, not speaking, incongruous affect), and marked social withdrawal. Schizophrenia is often a long-term illness that may last years and require long-term treatment, running a chronic deteriorating course with significant impairment in multiple areas of functioning (e.g. self-care, social relationship, work related). Often a FHx of mental illness.

Box 18.7 Features suggestive of organic psychosis or delirium

- Acute onset for first time within the preceding month.
- Assume new-onset 'psychosis' in the elderly is organic unless proven otherwise.
- ↓ level of consciousness.
- Disorientation to time, place, and person, worsening at night.
- Presence of medical illness (Box 18.6).
- Medications with CNS action, e.g. efavirenz, steroids, opioids.

Bipolar disorder (or manic-depressive illness)

Characterized by episodes of 'high' mood or mania, and 'low' mood or depression. Usually begins in adulthood and is generally diagnosed because of the manic phase, characterized by agitation, inappropriate behaviour (e.g. spending money excessively or sexually inappropriate behaviour), ↓ sleep, ↑ levels of energy, irritability, suspiciousness, rapid thinking and speech, and grandiose delusions (e.g. believing one has special powers). Depressed phase is similar to depression in common mental disorders, but usually more serious. A typical feature of this condition is that it is episodic. There are months–years when person is completely well, even off treatment. Often FHx of mental illness. Bipolar disorder diagnosis requires ≥1 manic episode. Differential diagnosis of manic episodes incl. alcohol or drug misuse, and acute psychoses.

Acute or brief psychoses

Usually start suddenly. Characterized by florid or marked psychotic symptoms. Most patients recover completely within a month and do not need long-term treatment. Typically caused by sudden severe stressful event (e.g. death of a loved person), or may be induced by amphetamines, cannabis, or prescribed drugs (e.g. mefloquine, chloroquine). Sometimes, acute psychotic episode may herald schizophrenia. Important to rule out delirium or organic psychosis.

Management of severe mental disorders

- If acutely disturbed, see ➲ Box 18.3, p. 772.
- Treatment should be started as soon as possible.
- Screen for risk of suicide (➲ Box 18.2 p. 770) and/or harm to self or others.
- Treat with antipsychotic medication (for schizophrenia, manic episodes, or acute psychoses) or mood-stabilizing medication (for bipolar

disorder). These medications are usually needed for extended period >12mths, and often for several years, depending on the response.
- Develop a therapeutic relationship with the patient.
- Review regularly to assess mental health and provide medication.
- Maintain realistic hope.
- If there is no or incomplete response, ↑ dose.
- *Assess adherence*: discuss reasons for non-adherence (e.g. poor insight, intolerable side effects) and address these reasons (e.g. switch antipsychotic drug to an alternative with fewer side effects).
- *Family intervention*: discuss the illness with supportive family members, and counsel them to ↓ levels of stress and hostility in the family. A sympathetic explanation that the patient is suffering from an illness that can be treated may help ↓ fears about the cause and implications of the illness. Emphasize that schizophrenia and bipolar disorder need long-term treatment.
- Advocate for persons with severe mental disorder to be brought for treatment if they relapse, rather than being restrained at home.
- Explain to family that covert administration of medication (e.g. hidden in food) may have long-term –ve effects on the patient's trust, and ultimately cause more harm than good.
- Encourage inclusion of patient in social activities and community.
- Once patient has recovered from acute symptoms, encourage participation in sheltered work or appropriate training to help develop occupational and self-care skills.
- Activity or distraction may ↓ severity or burden of symptoms (e.g. hallucinations).
- Esp. in bipolar disorder, emphasize importance of routine and avoid sleep deprivation, to ↓ risk of relapse.
- Discuss with patient and their family early symptoms of relapse and the importance of seeking treatment promptly.
- Counsel patient regarding cessation of substance abuse, esp. cannabis, amphetamine, and khat, which can ↑ psychoses.

Antipsychotic drugs for severe mental disorders

Antipsychotic drugs can be conveniently grouped into:
- *Conventional ('typical') drugs*: e.g. chlorpromazine, trifluoperazine, haloperidol. These drugs are older and more widely available, but have ↑ extrapyramidal/anticholinergic side effects.
- *Atypical drugs*: e.g. risperidone, clozapine. These are newer, have fewer extrapyramidal and anticholinergic side effects, but ↑ risk of metabolic syndrome (diabetes, hypercholesterolaemia, hypertriglyceridaemia, obesity); clozapine can → potentially serious bone-marrow suppressive side effects.
- *Depot medication*: long-acting, injectable formulations (conventional or atypical), e.g. flupentixol decanoate and haloperidol decanoate.

Starting dose

Start drug-naïve patients on a low dose and ↑ based on clinical response (e.g. haloperidol 0.5–3mg oral bd (3–5mg bd or tds if severe) ↑ to 15mg bd max.; or chlorpromazine 75mg oral single dose at night ↑ to 300mg max.; or risperidone 2mg oral single dose at night (4mg if severe), ↑ to max. 8mg at

night). Benefit should become apparent in <2wks and continued improvement occurs for 3–6mths. Consider depot medication if oral drug adherence is poor and relapses are frequent; always give a test dose (e.g. 12.5mg of fluphenazine decanoate, 25mg of haloperidol decanoate).

Length of treatment

For first-onset psychosis, antipsychotic drugs may be gradually ↓ after the patient has been well for >12mths. For schizophrenia, the medication may need to be continued, sometimes for many years. Depot medication may be esp. useful for these patients; a test dose of a depot must always be administered the first time the drugs are used.

Side effects

Warn patient about likely side effects. Acute and chronic movement disorders and anticholinergic effects for conventional drugs, ↑ appetite and ↑ weight, hyperglycaemia/diabetes, sedation, and hyperprolactinaemia (gynaecomastia, galactorrhoea, dysmenorrhoea, and sexual dysfunction).

Movement disorders

Incl. acute dystonia, which may occur within hours (e.g. painful ocular deviation, neck twisting, or muscle spasms); Parkinsonism (tremors and rigidity); and akathisia (severe motor restlessness). Movement disorders should be managed by:

- ↓ dose.
- Switching from a conventional to an atypical antipsychotic.
- Treat acute dystonias with an anticholinergic drug, e.g. procyclidine 5–10mg IM (repeated if necessary after 20min; max. 20mg daily).
- Treat Parkinsonism with an anticholinergic, e.g. procyclidine 2.5mg oral tds, ↑ gradually to max. 30mg in divided doses.
- Akathisia can be managed with a benzodiazepine or β-blocker.

Issues with treatment of schizophrenia

Most patients with schizophrenia respond to an antipsychotic; however, the majority will relapse >2yrs if they stop medication. 25% of patients do not respond adequately, despite being adherent. They should be switched to an alternative drug, ideally from a different class. Patients who remain psychotic despite adequate trials of antipsychotics are often termed 'treatment resistant'. The diagnosis should be reviewed. If the diagnosis is schizophrenia, a trial of clozapine is warranted (2/3 of patients will respond to clozapine). Withdraw other antipsychotics and commence clozapine 12.5mg oral od or bd initially, gradually ↑ to 300mg od over 2–3wks in 25–50mg increments (and thereafter up to max. 900mg daily). Monitor FBC weekly for 4mths initially, and monthly, thereafter (causes agranulocytosis). Monitor temperature, pulse, and BP daily during 1st week of treatment.

Mood stabilizers

These are drugs used to prevent episodes of mania or depression in people with bipolar disorder, as well as to treat acute relapse. Lithium and sodium valproate are most effective. Both must be taken regularly and require monitoring, especially lithium. Lithium is not recommended in absence of monitoring facilities. Maintenance with antipsychotic drugs (e.g. risperidone) may be necessary where mood stabilizers not available.

Lithium carbonate

Start at 400mg od and titrate dose (sometimes up to >1g/d) to achieve a serum lithium concentration 0.4–1.0mmol/L 12h after a dose 4–7d after starting treatment. *Note*: doses depend on preparation used. Preparations vary widely in bioavailability and dose. Blood levels should be measured weekly until stable, and then at least 6mthly. Warn patients about signs of toxicity: coarse tremor, nausea, diarrhoea, confusion, seizures; can → congenital malformations if taken by pregnant women. If preparation changed same precautions required as initiation of treatment. Seek mental health specialist advice if patient considering pregnancy or is pregnant.

Sodium valproate

This is an effective mood stabilizer and is effective for epilepsy, less toxic in overdose, and requires less blood monitoring. Start with 750mg daily in 2–3 divided doses and ↑ according to clinical response up to 1–2g/d in divided doses. The risk of teratogenicity is high, so should not be the first choice in women of reproductive age: if you do prescribe, give folate and advise contraception.

Disorders due to substance abuse

The most common substances of abuse/dependence are alcohol and tobacco. Others include:

- Inhaled glue or benzene.
- Heroin; cocaine.
- Amphetamines.
- Khat.
- Cannabis.
- Benzodiazepines.

The origin of benzodiazepine or opiate abuse is often iatrogenic. Alcohol and drug abuse is rarely the main reason for seeking health care. Instead, the HCW has to be alert to the possibility of substance abuse (e.g. repeated unexplained injuries or absence from work). Substance abuse ↑ risk of common mental disorders and suicide. Psychoses can occur—both during intoxicated and withdrawal states.

Intoxication and overdose

See ➲ Acute confusional state and delirium, p. 384 and ➲ Acute behavioural disturbance, p. 771 for medical management of acute confusional states and acute behavioural disturbance, and ➲ Acute poisoning with pharmaceuticals/chemicals p. 820.

Alcohol intoxication

Characterized by smell of alcohol on breath, slurred speech, and uninhibited behaviour. If ↓ level of consciousness, assess airway and breathing; place person on their side to prevent aspiration in case they vomit, and observe until effects of alcohol have worn off. If delirium, consider hypoglycaemia, head injury, subdural haematoma, infection (especially pneumonia), Wernicke's encephalopathy, delirium tremens (alcohol withdrawal), hypoxia, hepatic encephalopathy, cerebrovascular accidents, and post-ictal confusion (Box 18.8).

Sedative drugs

Overdose may ↓ level of consciousness, slow RR and → pinpoint pupils (in opioid overdose). See ➲ Acute poisoning with pharmaceuticals/chemicals, p. 820, for emergency medical management.

Stimulants

Look for dilated pupils, ↑ pulse, and BP, excited or disordered thoughts, paranoia, aggressive, erratic, or violent behaviour, and a history of recent consumption of cocaine or other stimulants.

- Give diazepam 5–10mg IV every 20–30min until calm and lightly sedated; monitor carefully and have flumazenil available to reverse benzodiazepine effect if over-sedated.
- If psychotic symptoms, and the patient does not respond to diazepam, give parenteral or oral antipsychotic medication.
- Monitor pulse, BP, and temperature every 2–4h.
- Chest pain may indicate tachyarrhythmias.
- Observe carefully for suicidal thoughts or actions after intoxication.

Box 18.8 Assessing alcohol abuse: CAGE questionnaire

Alcohol dependence or harmful use is likely if 2 +ve answers:

- Have you ever felt you should *cut* down your drinking?
- Have people *annoyed* you by criticizing your drinking?
- Have you ever felt bad or *guilty* about your drinking?
- Have you ever had a drink first think in the morning to steady your nerves or get rid of a hangover (*eye-opener*)?

Dependence and harmful use

Dependence

This is defined as the presence of ≥3 of the following:

- Strong desire/compulsion to take the substance.
- Difficulties controlling substance-taking behaviour in terms of onset, termination, or levels of use.
- *Withdrawal*: a physiological state when the substance has been stopped or reduced; the patient may use the substance to relieve or avoid withdrawal symptoms.
- *Tolerance*: ↑ doses are required to achieve a given effect.
- *Neglect of alternative interests*: obtaining and taking the substance gradually dominates the individual's life.
- Continued use despite user being aware of harmful consequences.

Dependence → great damage to individuals, their families, and the community, e.g. alcohol not only → physical harm to the drinker, but also ↑ suicide rates, relationship problems and domestic violence, road traffic crashes, and worsening economic circumstances.

Harmful use

This is substance abuse → significant damage to mental or physical health but not fulfilling the above-listed criteria. Harmful use may be defined by the quantity consumed (e.g. >2 standard alcoholic drinks/d over an extended period of time) or the pattern of use (e.g. >5 standard drinks/d at any time in the past year).

Management of dependence

There is ↑ evidence that dependent patients have ↓ ability to control substance use; it is not just 'a lack of willpower'. Ask 'open' questions and use 'reflective listening', clarify concerns, convey empathy, and, using these techniques, motivate patients to reach their own conclusions about adverse effects of substance use and the need to change their behaviour. Advise that dependence is an illness with serious health effects, and stopping or ↓ use will ↑ mental and physical health, social, and economic benefits. Explain symptoms of withdrawal. Abstinence should be goal in most cases.

Brief interventions can ↓ harmful and dependent use. Clearly explain the link between the patient's level of alcohol or drug use, their health (and other) problems, and short-term and long-terms risks of continuing use.

For patients willing to stop or control their use, help them:

- Set a definite day to quit/begin controlled use.
- Enlist the help of a buddy not using the substance to provide support.
- If reducing use, agree a clear goal for reduction (e.g. no more than 4U of alcohol/day and 2 alcohol-free days/wk).

- Agree strategies to control use (e.g. slow down drinking to <1U/h; introduce alternative behaviour, e.g. interspersing alcoholic drinks with non-alcoholic drinks, chewing gum, exercise).
- Remove substances from the home.
- Identify high-risk situations (social or stressful occasions) and strategies to avoid or cope with these.
- Make plans to avoid substances (e.g. ways to respond to friends who are using substances).
- Discuss symptoms and management of withdrawal (➲ Withdrawal states, p. 787).
- Medicines may be available for withdrawal from opiates (e.g. methadone); these need specialist assessment and monitoring.
- Minimize risk of harm due to substance abuse, e.g. advise not to drive after drinking, never to share needles, safe sexual practice.
- Prevent iatrogenic abuse by using benzodiazepines cautiously, and never for more than 4wks running.

If the attempt is successful consider medicines to ↓ risk of relapse:

- *Acamprosate*: ↓ craving for alcohol. Start immediately following withdrawal (weight 60kg, 666mg tds; <60kg, 666mg at breakfast followed by 333mg at midday and at night), continue for 12mths. Adverse effects occur in 20% of patients, most commonly GI disturbance and rash.
- *Disulfiram*: causes an unpleasant and potentially dangerous reaction when taken with alcohol. Fear of this reaction helps motivated individuals to abstain from alcohol. Prescribe 200mg daily and, with patient's consent, enlist caregivers to ensure adherence.

Relapse is common and often occurs because the person is not able to deal with life difficulties. Once drug use is stopped, discuss ways in which the person could cope. Identify different things a person can do to ↓ risk of taking drugs, such as giving up friends who use drugs; getting back to work, school, other enjoyable activities; learning relaxation and problem-solving; joining community groups which help substance users (e.g. Alcoholics Anonymous).

If the attempt is unsuccessful or relapse occurs:

- Praise any areas of success (e.g. cut down use for a period).
- Discuss situations/triggers for relapse; how can changes be made?
- Try again.

Withdrawal states

Physical effects common to many substances incl. anxiety, tremor, fever, sleep disturbance, tachycardia, GI disturbance. In addition, symptoms may occur during withdrawal:

- *Opiates*: hypertension, tachycardia, dysphoria, agitation, insomnia, diarrhoea, vomiting, shivering, sweating, lacrimation, rhinorrhoea, dilated pupils, piloerection ('gooseflesh'), muscle aches.
- *Alcohol*: seizures, confusional states incl. delirium tremens (severe confusion with visual/auditory hallucinations and paranoia); risk of Wernicke's encephalopathy (confusion, ataxia, nystagmus, ophthalmoplegia due to thiamine deficiency, ➔ Vitamin B_1 (thiamine) deficiency, p. 660).
- *Benzodiazepines/barbiturates*: ↓ weight, vivid dreams (rapid eye movement (REM) sleep rebound), tinnitus, irritability, ↓ memory and concentration, perceptual disturbance (hypersensitivity to sound, light and touch, de-realization and de-personalization), confusion, and seizures.

Withdrawal usually begins 4–12h after the last dose, peaks at 48–72h, and lasts 7–10d. Benzodiazepine withdrawal begins later, usually 1–14d after the last dose and lasting a few weeks (longer in a minority). The confusional states (delirium) following alcohol, benzodiazepine, and barbiturate withdrawal are potentially life-threatening and should be managed as described elsewhere (➔ Acute pesticide poisoning, p. 816). Seizures occurring in the context of withdrawal of alcohol or benzodiazepines should be managed with diazepam; do not start prophylactic anticonvulsant therapy. ↓ risk of withdrawal by a gradual reducing regimen and treat withdrawal rapidly when identified.

Management of specific withdrawal states

Alcohol withdrawal

- Consider admission, esp. if a history of previous severe withdrawals (e.g. confusion, fits), poor physical health (e.g. liver failure), or mental health (e.g. suicidal ideation).
- Give a benzodiazepine at reducing dose over 5–10d. Initial dose depends on alcohol intake and withdrawal symptom severity, e.g. chlordiazepoxide 10–40mg oral qds or diazepam 10mg oral qds. Higher doses may be required. For inpatients, dose and dosing interval may be adjusted according to symptoms.
- For patients with significant liver failure a short-acting drug may be used instead (e.g. lorazepam 1mg od or bd), or give an initial dose of diazepam 5–10mg stat and determine duration of action before prescribing further doses.
- Give thiamine 100mg tds oral (IV in delirium tremens) for 5d to prevent/treat Wernicke's encephalopathy (➔ Vitamin B_1 (thiamine) deficiency, p. 660).

Opiate withdrawal

Withdrawal is more successful if linked to a residential rehabilitation programme. First-line medical management for acute opiate withdrawal is as follows:

- *Buprenorphine*: 0.8–4mg sublingual on 1st day, ↑ if necessary by 2–4mg daily to usual dose 12–24mg (max. 32mg) daily. Withdraw gradually over 3–14d. First dose should not be given until experiencing withdrawal symptoms (8h after last heroin dose, 24–48h after last methadone dose) due to risk of precipitating withdrawal.
- *Methadone*: initial dose 15–20mg oral, ↑ to 30mg/d and tapered over 3–10d.
- *Clonidine*: 0.1–0.15mg tds; or *lofexidine* 0.2mg bd (max. 1.2mg bd); withdraw over 2–4d; max. duration 10d. Side effects incl. lightheadedness and sedation.
- Take care with all these drugs if also taking sedative medications.
- Do not give opiate substitutes if the patient has been away from the ward and you suspect illicit drug use.
- Treat nausea, aches, and pains symptomatically. Monitor BP.

Most require maintenance opioid substitution therapy with buprenorphine or methadone. Take care when helping a patient to withdraw from opiates; following withdrawal, tolerance to opiates will ↓ and the patient can overdose if they resume use at the previous level.

Benzodiazepine withdrawal

Withdrawal is most common with short-acting agents, e.g. lorazepam.

- Change to an equivalent dose of a long-acting benzodiazepine, e.g. diazepam (lorazepam 0.5–1mg is equivalent to diazepam 5mg).
- Then gradually ↓ dose every 2–3wks in steps of diazepam 0.5–2.5mg depending on initial dose and duration of treatment.
- If withdrawal symptoms occur, maintain dose until symptoms improve. Thereafter ↓ dose further, in smaller steps if necessary.
- If dependency is chronic, this may take months.

Adjustment disorders and bereavement

A state of emotional disturbance and impaired social functioning may develop shortly (<3mths) after or during a stressor.

There may be affective, cognitive, and behavioural symptoms. Stressors may be, e.g. disasters or traumatic events, bereavement, diagnosis of a major illness such as HIV/AIDS, migration. Adjustment disorders are common in people with physical disorders, and should be considered if rehabilitation is slower or poorer than expected.

Bereavement

May be abnormal in form and/or severity compared with cultural norms. Four stages have been described:

- Shock and numbness.
- Preoccupation (yearning or anger, etc.).
- Disorganization (loss is reluctantly accepted).
- Resolution.

These may not necessarily occur in this order. Bereavement is considered abnormal when symptoms are not related to the loss, e.g. feelings of worthlessness or inappropriate guilt or if the symptoms last beyond a reasonable period of time and → significant social impairment. Abnormal perceptions involving the lost person (e.g. hearing them whispering) can be a feature of normal bereavement, but hallucinatory phenomena not involving the lost person are indications of abnormal (or pathological) bereavement.

Management

- Allow (but do not push) individual to talk about loss and its circumstances, and to discuss feelings provoked, especially guilt and anger.
- Support culturally appropriate mourning.
- Involve others in family, and aim to ↑ social support/reactivate social networks.
- Identify steps that can be taken to modify causes of stress.
- Medication should be avoided unless there is depression or psychosis. If there is severe insomnia, hypnotics may be used for <2wks, e.g. diazepam 10mg at night, promethazine 25mg at night.

Post-traumatic stress disorder

An incident that makes a person fear for their life or causes extreme distress is a traumatic event (e.g. rape, war, major disasters). Many persons affected by trauma will experience some emotional reaction—feelings of being numb or in a daze, fear, insomnia, repeated thoughts of the event, irritability, nightmares, and ↓ concentration. This is a normal response and lasts typically 2–4wks. In a few people, however, these experiences continue for months or years after the trauma, interfering with daily life and → alcohol abuse or problems in relationships. This is called post-traumatic stress disorder (PTSD).

Clinical features

- Experiencing trauma repeatedly through intrusive and distressing visions of incident, nightmares, and 'flashbacks'.
- Avoiding situations that remind him/her of traumatic incident.
- He/she is unable to remember things related to trauma and feels emotionally distant from people.
- ↑ *arousal*: sleep is disturbed, patient feels irritable, has difficulty concentrating, and is easily startled or scared.
- Panic attacks may occur.
- Many patients with PTSD feel depressed and lose interest in daily life, feel tired, or suffer aches and pains, and have suicidal feelings.

Management

- Allow, but do not push, patient to talk about what happened and assess their needs and concerns.
- Ensure physical needs are met, and that patient is protected from further harm.
- Support culturally appropriate adjustment to what happened.
- Reassure that emotional reactions are normal, not madness.
- Encourage patient not to avoid situations that remind them of event. As far as possible, encourage normal routine and getting back to usual activities.
- Victim should not be left alone for some days. Make sure that they are staying with caring relatives or friends.
- For panic attacks, follow steps suggested previously (➲ Panic disorder, p. 777).
- For acute severe symptoms, use benzodiazepines for up to 2wks.
- A course of antidepressants may help some patients.

Intellectual (learning) disability

Intellectual disability (ID) is a developmental disability, not a mental illness. Child's mental abilities are slower/delayed compared with other children, with impairment in cognitive, social, language, and motor development. Prevalence of moderate to severe ID varies from 1/1000 to 20/1000 worldwide. Persons with ID are often brought to HCWs by concerned family members for many reasons, including self-care, school difficulties, and behavioural problems, e.g. aggression.

Clinical features

- Delays in milestones, e.g. sitting, walking, speaking.
- Difficulties in school, e.g. coping with studies and repeated failure.
- Difficulties in relating to others, esp. children of same age.
- In adolescents, inappropriate sexual behaviour.
- In adults, problems in everyday activities, e.g. cooking, managing money, finding and staying in a job.

There are degrees of ID:

- *Mild ID*: may → difficulty in schooling but no other problems.
- *Moderate ID*: may → failure to stay in the school system and difficulties in self-care, e.g. bathing.
- *Severe ID*: often requires help for simple activities, e.g. feeding.

A person with mild ID may spend their entire life without being 'detected'; those at severe end are diagnosed in early childhood because of obvious severity of disability. People with mild ID may be able to live alone and work in certain jobs; however, severely affected people need close supervision and care.

Assessment

- An informant, e.g. a parent, is essential.
- Record nature and extent of ID—take developmental history and assess delay in communication and social interaction; motor function and self-care; and functional academic skills.
- Identify problems, e.g. self-harm or harm to others; impulsive or dangerous behaviour.
- Determine aetiology, see Box 18.9. In most cases, no definite aetiology will be identifiable.
- Identify coexisting psychiatric diagnoses, e.g. psychoses. Prevalence is 2–4-fold higher in people with ID than the general population.

Box 18.9 Causes of moderate to severe ID

- *Prenatal (50–70%)*: genetic (e.g. fragile X, Down's syndrome), congenital infections (e.g. HSV, rubella, HIV, toxoplasmosis, syphilis, CMV), exposure to toxins (e.g. alcohol), maternal disorder (e.g. pre-eclampsia).
- *Perinatal (10–20%)*: LBW, extreme prematurity, birth asphyxia or brain trauma, neonatal sepsis, encephalitis, kernicterus.
- *Postnatal (5–10%)*: brain damage due to trauma, infections, toxic agents (e.g. lead poisoning), iodine deficiency, malnutrition.

Management

- Be certain that the child has ID. This implies that the child has incurable and life-long disability. It is a label that can cause great unhappiness, so use it with care. If in doubt, get a second opinion from a specialist.
- Once you are confident that the child has ID, determine the severity. The abilities a child has will be an important indicator of how much progress they are likely to make in years ahead.
- Screen for contributory medical problems, e.g. hypothyroidism, sensory impairment, seizures, chronic infection, malnutrition.
- Other than these rare situations, there are no indications for using medicines to treat ID. Do not use 'brain tonics' and other medicines supposed to help 'mental function'. Use antipsychotics or antidepressants to treat psychoses or common mental disorders. Do not use medication to treat behavioural disturbance.
- Reassure family that, even though the child has limited mental abilities, he/she will achieve many milestones in life. They must be prepared to accept a delay in these milestones and be realistic in what they expect their child to achieve. Explain that there is no cure and that they should not waste money on false claims of cures.
- Teach parents how to help the child in daily activities, e.g. toileting and feeding, breaking down activities into smaller bits.
- Use reward and praise whenever the child succeeds in any activity, however small. Find activities that can help parents spend time with the child, and yet allow other household activities to be done, e.g. child could learn to help with daily chores.
- Never ignore the child's educational needs. Some parents feel like giving up on their child's education when they discover that they have ID. Explain that their child needs education, just as any other child. Refer the family to local schools for children with special needs. Avoid institutionalization.
- Provide information about any special schemes to help families with children with ID, either through financial or educational help.
- Stay in regular touch with the family. Children with ID often need guidance about their reproductive and sexual health, when they become adolescents. Some families go through a lot of stress because of caring for a child with ID, especially when severe. Caring can → stress and mental health problems. Refer parents to support groups and offer treatment for common mental disorders *if needed*.

Disorders in children and adolescents

In younger children, most common and disabling disorders are developmental. If a child has behavioural problems or difficulties in school, take a developmental history first to rule out ID. Once ID has been ruled out, consider the possibility of:

- *Autism and other pervasive developmental disorders*: characterized by delays or loss of language abilities and marked impairment in social relationships; typically present in early to mid-childhood. These disorders require a similar approach to that described for ID.
- *Attention deficit and hyperactivity disorder*: marked by impulsivity, hyperactivity, and poor concentration; typically presents in primary school. Children with this disorder may benefit from parent and teacher guided behavioural treatments and medication (methylphenidate—only to be used by experienced child or mental health practitioners).
- *Specific learning disabilities*: impairment(s) in specific learning and cognitive abilities, e.g. reading and writing (dyslexia); typically presents when child is in secondary school. Remedial education within mainstream schools is 1° intervention.

In adolescents, emotional and behavioural disorders linked to difficulties in school or at home are common. The most common mental disorders are depression, substance abuse, psychoses, and conduct disorders (antisocial behaviours). Mental health problems in adolescents may be managed similar to adults.

Child abuse

Child abuse is present in most societies, and more widespread than thought previously, although prevalence is not known. Children can be abused physically, emotionally, or sexually, affecting their health and development. Both boys and girls can be abused, most often by someone they know well. Abused children may have problems with:

- *Physical health*: bruises or cuts, fractures, cigarette burns; severe cases can → death.
- *Sexual health*: injuries to sexual organs, pregnancy, and STIs.
- *Mental health*: fear, aggression, ↓ concentration, bed-wetting (having previously had control), depression, antisocial behaviour, self-harm.
- *School performance*: ↓ school performance.

Diagnosis

- *Ask family*: few adults will openly report that they feel a child they know is being abused. If child abuse suspected, it is essential that you ask the adult in a frank and open way if they think the child is being physically, emotionally, or sexually hurt.
- *Ask the child*: interview the child with their mother, or another adult who is definitely not a suspected abuser, whom the child trusts. Do not ask questions about abuse until you have established a rapport with the child. This may require spending more time. Ask: 'Sometimes, children can get hurt by a grown-up person. Has anyone grown-up hurt you recently?' Do not force the child to answer.

- *Examine the child*: a child who has been abused is likely to be very sensitive to being examined physically. Respect child's privacy. Explain what you are doing and why. Have a trusted family member present during examination. Document findings in detail. These may be needed in a police investigation. A thorough examination of the child should include weight and height, injuries on body, and injuries or inflammation of sexual organs, including anus.

Management

- *Your priority is the health and safety of the child*: if you suspect the child's life is in danger, refer immediately to a place of safety.
- *Talk to the family members*: explain why you suspect abuse. Many parents are not aware that their actions can be so damaging to the child's health. Just telling them about the dangers of beating a child or neglecting emotional needs may → change in their behaviour.
- It is unlikely that the family will accept sexual abuse easily, especially if the abuser is someone close to the family. Do not accuse anyone. Instead, share your concerns openly with the family and stress that if abuse continues, the child's health will be even more seriously affected.
- *Teach the child how to ensure their safety*: explain that the abuse is not their fault and they should not feel guilty for having spoken out about it. Important to make sure this never happens again. Some suggestions on how to prevent abuse from recurring are:
  - To tell the abuser firmly not to touch her.
  - To run away from the abuser.
  - To be with another adult who can protect her.
- *Put the family in touch with community supports*: e.g. child support groups, family violence groups, legal support, child protection agencies, the police, or specialist health professionals.
- If the child abuse persists or is very serious, refer to specialist team.
- Keep in close touch with child and family at regular intervals for at least 6mths. Very often, abuse stops once it has been openly discussed. If it does not, you may need to encourage family to take action to stop it. Talk to the child each time; many children do recover from the trauma, but some children will develop mental health problems.

Further reading

World Health Organization (2016). mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP). Version 2. Geneva: World Health Organization. Available free from: https://www.who.int/publications/i/item/mhgap-intervention-guide---version-2.0

Chapter 19

Trauma

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Primary assessment in trauma

Major trauma remains a leading cause of death globally, especially in LMICs. Improved pre-hospital care and better trauma referral services → better outcomes; in resource-poor settings, basic trauma management remains most important.

Primary assessment: ABCDE

The ABCDE system allows rapid systematic assessment and simultaneous treatment of life-threatening injuries. Do not move on to the next system until the current problem is treated. If the patient deteriorates, go back to the beginning and assess again**.**

The following should → full trauma assessment:

• **A**irway:	• Can the patient talk and breathe freely? If available, give supplemental O_2.
• **B**reathing:	• Is the patient breathing (look, listen, feel)? Is breathing adequate?
• **C**irculation:	• Can peripheral or central pulses be felt? Is capillary refill <3s?
• **D**isability:	• Use the AVPU scale (➲ Chapter 1, Box 1.6, p. 7).
• **E**xposure:	• Undress the patient and look for injury.

History

- Fall >3m.
- Motor vehicle accident (MVA) at >30km/h.
- Thrown from vehicle/trapped in vehicle.
- Death of a person in accident.
- Patient is a pedestrian involved in MVA.
- MVA involving car/cycle or car/unrestrained occupant.

Examination

- Airway problem or respiratory distress.
- BP <100mmHg.
- GCS score <13/15.
- >1 area injured.
- Penetrating injury.

Further reading

The following publications are free to download and provide further detailed guidance on trauma management and the resources required in low-resource settings:

Wilkinson DA, Skinner MW (2000). *Primary Trauma Care: A Manual for Trauma Management in District and Remote Locations*. Oxford: Primary Trauma Care Foundation. Available at: 🔗 www.primarytraumacare.org/wp-content/uploads/2011/09/PTC_ENG.pdf.

World Health Organization (2004). *Guidelines for Essential Trauma Care*. Geneva: WHO. Available at: 🔗 http://whqlibdoc.who.int/publications/2004/9241546409.pdf.

Airway

Assessment

If the patient can speak clearly, assume they have a patent airway and are breathing adequately.

Signs of airway obstruction are often subtle and include:

- Abnormal respiratory sounds: stridor, snoring, gurgling.
- Signs of ↑ work of breathing: nasal flaring, rocking abdominal movements, use of accessory muscles of respiration +/− tracheal tug.
- Cyanosis and agitation are late signs and represent hypoxia.
- If the patient is apnoeic, consider an obstructed airway.

Predicting imminent loss of airway is difficult if none of the above-listed signs are present (e.g. in the case of burns). In these situations, first complete the full 1° assessment and exclude other life-threatening injuries. If signs of airway obstruction do develop, immediately revert back to the airway assessment and manage appropriately.

Management

The level of operator skills and equipment available will determine the safest intervention. Always consider cervical spine injury and apply manual in-line immobilization where appropriate.

- *Simple airway management*: chin lift/jaw thrust; oropharyngeal suction; oropharyngeal or nasopharyngeal airway (avoid nasopharyngeal airway if base-of-skull fracture possible/suspected).
- If these manoeuvres do not help or the patient becomes apnoeic, hypoxic, unconscious, or has severe head, chest, or neck trauma, → advanced airway management.
- *Advanced airway management*: endotracheal intubation; surgical airway—cricothyroid puncture or tracheostomy depending on equipment, skill, and resources. These also protect from large volume aspiration of oropharyngeal contents, e.g. gastric aspiration.
- *Laryngeal mask airways*: these are useful if airway support is required and endotracheal intubation is not possible, or unsafe.

Any of these airway manoeuvres require adequate training and, particularly with surgical airways, may be fatal if attempted by inadequately trained personnel.

Breathing

Once airway patent, next ensure adequate ventilation.

Assessment

- *Is the patient breathing*: *look* for chest rise and fall, *listen* for breath sounds at the mouth, and *feel* for chest movement and air movement at the mouth.
- *Assess adequacy of ventilation*: signs of inadequate ventilation may be very subtle—rapidly but carefully perform a clinical assessment:
  - *Look* for signs of respiratory difficulties, noting respiratory rate and pattern. Use of accessory muscles, irregular breathing pattern, and cyanosis; or obvious extensive chest injury (e.g. penetrating injury, flail chest, or a sucking injury) → immediate need for ventilatory support or intervention.
  - *Listen* for ↓ or absent breath sounds—may indicate pneumothorax or haemothorax. Resonance (pneumothorax) or dullness (haemothorax) to percussion are often difficult in a stressful trauma setting. Pneumothorax and haemothorax are very difficult to diagnose clinically, and normal clinical examination does not exclude them.
  - *Feel* for tracheal shift, broken ribs, and subcutaneous emphysema.
  - If telemetry is available, peripheral plethysmography may be very useful. O_2 desaturation is a late event and urgent interventions are often required despite normal O_2 saturations.

Management

Interventions during the 1° survey are aimed at recognizing and treating life-threatening injuries:

- Tension pneumothorax.
- Flail chest.
- Open/sucking chest wound.

See ➲ Chest trauma, p. 803.

Circulation

Assessment

The following may indicate adequate circulation:

- Being alert (adequate brain perfusion).
- Passing urine (adequate renal perfusion).
- Capillary refill time <2s (adequate peripheral perfusion).

Note, that these signs are often unreliable in the trauma setting, due to the neurohormonal response to injury and because trauma patients are often young and can compensate for significant cardiovascular shock, appearing deceptively well until the point of decompensation.

A systematic approach to assessing the circulation should include:

- *Inspection of peripheries*: skin condition, colour, temperature, pallor, presence/absence of pulses, capillary refill time.
- *Secure IV access*: if not rapidly successful, urgently call for senior help. Consider early intraosseous line placement in both children and adults. Although venous cut-down of the greater saphenous vein has fallen into disfavour in many trauma centres, this may be faster than the intraosseous route if equipment is lacking.
- *Perform baseline bloods and blood typing* if available.
- *BP and pulse rate* are useful in diagnosing shock and tracking response to therapy, and should be monitored.
- *Bleeding* may be obvious or concealed. Obvious bleeding should be addressed early (Box 19.1). Use compression dressings and tourniquets if necessary. Signs of concealed bleeding are not specific, but if there is ongoing shock despite resuscitation, consider the following common sites of concealed bleeding:
  - Long bone fractures.
  - Pelvic fractures.
  - Major vascular injuries with retroperitoneal bleeding.
  - Intrathoracic bleeding.

Management

A cause for shock should be sought, with the intention of addressing this and restoring O_2 delivery to tissues. If haemorrhage is the cause, urgently stop or slow ongoing bleeding. Administer two doses of tranexamic acid if presenting within 8h of injury: 1g immediately and 1g as an infusion over 8h.

Volume replacement and warming

Aggressive fluid resuscitation is controversial. Some of the drawbacks include hypothermia, metabolic and electrolyte derangements, as well as dilutional coagulopathy. However, early crystalloid resuscitation (up to 30mL/kg) when indicated still forms a useful part of the management of injured patients (see the following list).

Important principles relating to fluid resuscitation in trauma include:

- *Warm fluid replacement*: hypothermia → organ dysfunction and coagulopathy. Even in warm climates, trauma patients can quickly become hypothermic. IV and oral fluids should be warmed to 40–42°C.
- *Hypotensive fluid resuscitation*: if haemostasis not complete, aim for relatively low systolic BP of 80–90mmHg until definitive haemostasis can be achieved. This will help ↓ further blood loss.

- *Blood transfusion*: the optimum threshold for transfusion in trauma is unknown. Consider transfusion when there is persistent shock despite fluid resuscitation, or when Hb <7g/dL with ongoing bleeding. If cross-matched or type-specific blood is not available, use O –ve packed red cells.
- *Other blood product support*: if there is a need for RBC transfusion it is likely that plasma and platelets will be required as well. The ratio in which these are administered is controversial—a rough guide of 1–1–1 is advocated by some. Patients' families or friends may be able to donate blood for them, but beware of incompatibility and blood-borne infections.
- *Per-oral fluid resuscitation*: safe and efficient if the patient has a gag reflex and is without abdominal injury. Use appropriate rehydration fluid (➲ General management of dehydration, p. 235).

Causes of shock following trauma

Shock in the trauma patient is usually due to haemorrhage and hypovolaemia, but can occur from other causes.

Haemorrhagic (hypovolaemic) shock Due to acute loss of blood or fluids. Easy to underestimate blood loss (Table 19.1), and large volumes may be concealed. In young, fit patients, signs of blood loss may not be obvious until >1L has been lost.

Treatment Fluid resuscitate and control bleeding.

Cardiogenic shock May be due to myocardial contusion; penetrating wound to heart; cardiac tamponade; MI; or tension pneumothorax (preventing venous return). Assessment of JVP and ECG may be helpful.

Treatment Treat cause; inotropes very rarely indicated.

Neurogenic shock Classically presents as hypotension with no reflex tachycardia or skin vasoconstriction. Cause is loss of sympathetic tone 2° to spinal cord injury.

Treatment Fluids, vasoconstrictors, spinal stabilization +/− surgery. Exclude other causes of shock.

Septic shock Rare in early phase of trauma but common in the days or weeks following injury. Occurs most commonly following penetrating abdominal injuries and burns. Common cause of late death in trauma.

Treatment Treat sepsis early (➲ Sepsis, p. 678), support organs.

Box 19.1 Strategies to stop bleeding

- *Limb injuries*: place gauze packs under fascia, manually compress proximal artery, apply compressive dressing to entire injured limb.
- *Chest injuries*: chest wall arteries are most common source of bleeding. Place intercostal chest drain and give pain relief. The expanded lung should tamponade bleeding.
- *Abdominal injuries*: *damage control laparotomy* is required as soon as possible if fluid resuscitation fails to → systolic BP of 80–90mmHg. It is not a surgical procedure, but a resuscitative one, involving gauze packing of bleeding abdominal quadrants and temporary closure of abdominal wound with towel clamps. The procedure should be observed before being done, but with training should be within the capabilities of a doctor or nurse; carry out under ketamine anaesthesia. Done properly, damage control laparotomy can save lives.
- *Pelvic fractures*: stabilize the pelvis by tying a sheet around pelvis if commercial devices not available.

Table 19.1 Indicators of blood loss in an adult

Blood loss	Up to 750mL	750–1500mL	1500–2000mL	>2000mL
Heart rate	<100	>100	>120	>140
BP	Normal	Systolic normal	↓	↓
Capillary refill	Normal (2s)	Prolonged	Prolonged	Prolonged
Respiratory rate	Normal	20–30/min	30–40/min	>40/min
Urine volume	>30mL/h	20–30mL/h	5–15mL/h	<10mL/h
Mental state	Normal	Mild concern	Anxious or confused	Coma

Secondary survey

Only proceed to 2° survey when patient's ABCDE is stable. Ideally this should be within minutes to hours following admission, but may be deferred if stabilization and/or surgery are required. If any deterioration occurs during the 2° survey, repeat the 1° survey to find and treat the problem before completing the 2° survey**.** The 2° survey comprises a thorough head-to-toe examination. During this part of the trauma evaluation there should be time to gather a complete medical history. Document all procedures undertaken.

Head examination

Scalp and ocular abnormalities; external ear and tympanic membrane injury; base-of-skull fracture (CSF leakage, periorbital ecchymosis); periorbital soft tissue injuries.

Neck examination

Penetrating wounds; subcutaneous emphysema; tracheal deviation; neck vein appearance.

Neurological examination

Assess using GCS (➲ Glasgow Coma Scale, p. 387); pupil size and response to light, spinal cord motor activity; sensation and reflex. Priapism and loss of anal sphincter tone may point to a spinal cord injury. A full log roll and examination of the back and vertebrae is essential.

Chest examination

Clavicles and all ribs; breath and heart sounds; ECG monitoring (if available). Contusions, 'seat-belt' sign and small penetrating wounds may point to severe internal trauma.

Abdominal examination

Surgical exploration is required for penetrating wounds. Blunt trauma mandates careful clinical consideration for laparotomy. Serial clinical examinations are not always accurate but remain essential. If available, focused abdominal USS or CT scan are most helpful. Insert NGT (except in presence of facial trauma); rectal examination; consider urinary catheter (check for urethral meatal blood before insertion).

Pelvis and limbs

- Examine peripheral pulses and for fractures, cuts, bruises, minor injuries.

X-rays (if possible and where indicated)

- Chest, lateral neck, and pelvis X-rays may be done during 1° survey.
- Cervical spine films (important to see all seven vertebrae).
- Pelvic and long bone X-rays.
- Skull X-ray may reveal fractures if head injury without focal neurological deficit, but is seldom indicated.
- CT should be used as appropriate where available.

Chest trauma

~25% of trauma deaths are due to thoracic injury.

Rib fractures

Clues to serious underlying injuries are fractures to multiple ribs, the first rib, and sternum. Important lung complications of rib fractures are:

- Acute: pulmonary contusion, pneumothorax, haemothorax.
- Delayed: pain → poor cough/respiratory effort → atelectasis, pneumonia.
- Rib fractures stabilize in ~2wks; firm healing with callus takes ~6wks.

Flail chest

If ≥2 consecutive ribs are fractured in ≥2 places → unstable chest wall segment that moves paradoxically in opposite direction to rest of thoracic cage during respiration → severe respiratory compromise. *This is a medical emergency*—treat with positive pressure ventilation and analgesia.

Tension pneumothorax

Injury → air entering but unable to exit pleural space → progressively ↑ intrathoracic pressure that may ↓ venous return to heart. Often presents with extreme pain and CVS instability; often fatal.

Urgent needle decompression is required: insert a large bore canula into the second intercostal space in the mid-clavicular line on the affected side to decompress. A hiss of decompressed air may occur, but is not always present. Definitive chest drain insertion in the fourth or fifth intercostal space, mid-axillary line is essential.

Haemothorax

Common in penetrating injures to chest; requires large-bore chest drain. Haemothorax of 500–1500mL that stops bleeding after insertion of intercostal drain can generally be treated in this way; haemothorax of >1500–2000mL or with continued bleeding >200–300mL/h is classed as a massive haemothorax and may require thoracotomy.

Pulmonary contusion (bruising)

Common after chest trauma; onset of symptoms can be slow. Most likely following high-speed crashes or falls from a great height. Clinical features include shortness of breath, hypoxaemia, tachycardia, absent breath sounds, rib fractures, and cyanosis. Presentation similar to pneumonia; ventilatory support may be required.

Open, 'sucking' chest wounds of the chest wall

Lung on affected side collapses. A seal (e.g. a square of plastic taped down on three out of four sides) is often sufficient to stop sucking and allow re-expansion; intercostal drains and intubation may be required.

Other thoracic injuries

Myocardial contusion, pericardial tamponade, injuries to thoracic great vessels, rupture of trachea or major bronchi, trauma to oesophagus, and diaphragmatic injuries can all occur. These are less common, but often fatal.

Abdominal trauma

Suspect abdominal injury in any patient involved in serious accident—unrecognized abdominal injury remains a frequent cause of preventable death. There are two categories:

- *Penetrating trauma*: e.g. gunshot, stabbing—liver injury common.
- *Non-penetrating trauma*: e.g. acceleration/deceleration, compression, crush, and seat belt injuries—splenic injury/rupture common.

~20% of trauma patients with acute haemoperitoneum (blood in abdomen) have no signs of peritoneal irritation at the first examination. Blunt trauma can be very difficult to evaluate, esp. in unconscious patients. Repeated 1° survey and serial abdominal examinations are required.

Complete examination of the abdomen includes rectal examination (sphincter tone, integrity of rectal wall, blood in rectum, prostate position). Check for blood at external urethral meatus. Catheterize (cautiously if pelvic injury suspected) to decompress the bladder and monitor urine output.

In women, exclude pregnancy. The best treatment for the fetus is resuscitation of the mother; occasionally, a pregnant mother at term may require delivery of baby to ensure she is adequately resuscitated (➲ Pregnant trauma patients, p. 811).

Diagnostic peritoneal lavage

USS by a trained operator can reliably detect free fluid in the abdomen. If USS not available, diagnostic peritoneal lavage involves putting a peritoneal catheter into the abdomen through a small umbilical incision and infusing 1L of warmed fluid. After a short period, fluid drains out by gravity and may be visually assessed for presence of blood or bowel contents. Relative contraindications for diagnostic peritoneal lavage include operator inexperience, pregnancy, previous abdominal surgery, and if result will not change management. If in doubt, laparotomy is still the gold standard.

Pelvic fractures

These are often complicated by massive haemorrhage and urological injury. Examine rectum for position of the prostate, presence of blood, and rectal/perineal laceration.

Management Resuscitation and immobilization, analgesia, transfusion, +/− surgery.

Head trauma

Early assessment and treatment of head-injuries is essential. Hypoxia and hypotension ↑↑ mortality. The following are potentially life-threatening, can sometimes be diagnosed clinically, and require urgent surgical decompression by burr-hole (➲ How to do a burr hole, p. 422):

- *Acute extradural haematoma*: typically presents as rapid ↓ level of consciousness following a lucid interval, often due to tearing of the middle meningeal artery → acute ↑ ICP. Contralateral hemiparesis and ipsilateral dilated pupil are suggestive signs.
- *Acute subdural haematoma*: tearing of bridging vein between cortex and dura, usually with clotted blood in the subdural space. Suspect severe contusion of the underlying brain tissue.

The following conditions can be treated conservatively as neurosurgery does not usually improve outcome:

- Base-of-skull fractures: suggestive signs include bruising of eyelids (periorbital ecchymosis) or over mastoid process (Battle's sign), or CSF leak from ears/nose.
- Cerebral concussion: temporarily altered consciousness.
- Depressed skull fracture: impaction of fragmented skull that may penetrate underlying dura and brain.
- Intracerebral haematoma: may result from acute injury or progressive damage 2° to contusion.

Always seek a neurosurgical opinion if available; occasionally, surgical intervention may be an option.

Management

Basic medical management for severe head injuries

- ABCDE 1° survey with cervical spine control.
- Record GCS score: <8 severe head injury; 9–12 moderate; 13–15 minor.
- Intubate if GCS score ≤8 (sometimes at higher score for transfer).
- Ventilate to normocapnia (PCO_2 4.5–5kPa if ABG available).
- Sedate with paralysis as necessary; avoid coughing and straining.
- Moderate IV fluid input, avoiding fluid overload.
- Nurse head up at 20 degrees.
- Prevent hyperthermia.

Deterioration may occur 2° to bleeding or cerebral herniation

Signs of ↑ ICP include unequal or dilated pupils, ↓ HR, ↑ BP, ↓ RR. Urgent management includes:

Hyperventilation: ↓ cerebral blood volume and may be effective for short periods e.g. if signs of herniation (↓ HR, single dilated pupil).

Osmotherapy with mannitol or hypertonic saline.

Hypotension primarily caused by brain injury is usually a catastrophic event (e.g. herniation, irreversible injury). This is a diagnosis of exclusion—bleeding and other causes of shock should be actively sought.

Spinal trauma

Injuries to the cervical spine and T12–L1 are common, as are injuries to brachial plexus and nerves to legs and fingers. In addition to sensory and motor loss, *neurogenic shock* (due to sympathetic loss to limbs and internal viscera below the level of the injury) can → hypotension and bradycardia (cf. 'spinal shock', which is abnormal neural function due to a 'stunned' spinal cord).

Management

Always examine spinal injury patients in the neutral position (supine without flexion, extension, or rotation) and without any movement of the spine. The patient should be log-rolled to move (i.e. moved by several people, working together to keep neck and spine immobilized); their neck immobilized with a stiff cervical neck collar or sandbags; and transported supine (Box 19.2).

Vertebral injury

May be associated with a spinal cord injury. Search for local tenderness, deformities including a posterior 'step-off' injury, and swelling.

Cervical spine injury

Look for respiratory compromise (diaphragmatic/paradoxical breathing); ↓ muscle tone; absent reflexes (check rectal sphincter); priapism and hypotension with bradycardia.

C-spine X-ray

Anteroposterior and a lateral X-ray (showing all seven cervical vertebrae) with a view of the atlas-axis joint. CT if available is far more accurate than plain X-ray.

Box 19.2 Neurological assessment of spinal trauma

Assess sensation and ask patient to make small movements.

Motor response	*Level*	*Sensory response*	*Level*
Diaphragm intact	C3, C4, C5	Anterior thigh	L2
Shrug shoulders	C4	Anterior knee	L3
Biceps (flex elbows)	C5	Anterolateral ankle	L4
Extension of wrist	C6	Dorsum big + 2nd toe	L5
Extension of elbow	C7	Lateral side of foot	S1
Flexion of wrist	C7	Posterior calf	S2
Abduction of fingers	C8	Perianal sensation	S2–5
Active chest expansion	T1–T12		
Hip flexion	L2		
Knee extension	L3–L4		
Ankle dorsiflexion	L5–S1		
Ankle plantar flexion	L1–S2		

Note: if there is no sensory or motor function with complete spinal cord lesion, chance of recovery is small.

Limb trauma

Examination

Examine skin colour, temperature; distal pulses; grazes, bleeding sites; limb alignment/deformities; active, passive, and unusual movements; crepitation; pain out of proportion to degree of injury.

Management

Maintain peripheral blood flow; prevent infection, skin necrosis, and damage to peripheral nerves.

Beware tourniquets

Tourniquets may be left on by mistake → marked ischaemic damage. If possible, stop active bleeding by direct pressure. Tourniquets are acceptable if bleeding not controlled by pressure dressings alone—they can ↓ overall blood loss.

Compartment syndrome

Caused by ↑ pressure in fascial compartments due to IM haematoma, crush injuries, fractures, or amputations. Compression of vessels and peripheral nerves → ↓ local circulation. ↓ Tissue perfusion can → muscle necrosis even if BP is normal. Forearm and lower leg compartments are at particular risk.

Clinical features

- Pain more than expected from injury.
- Tense compartments.
- Passive stretch test—pain on moving foot or lower limb.
- Paraesthesia.
- Pulse lost—a late sign.

If there is local hypoxaemia for >2h, reperfusion can → extensive tissue damage.

Management Decompress early by surgical fasciotomy.

Traumatic amputation

Cover traumatically amputated body parts with moistened sterile gauze towels and put in sterile plastic bag for cooling. Non-cooled amputated parts may be reattached <6h later; if cooled, up to 20h.

Rhabdomyolysis

Extensive muscle injury that may accompany any degree of trauma. If patient immobile for an extended period of time and/or hypothermic, extensive rhabdomyolysis may be present despite relatively minor trauma. Leakage of intracellular proteins into the circulation may → renal failure.

Diagnosis Clinical suspicion, ↑ serum CK. If CK not available, urine dipstick positive for blood supports the diagnosis as dipstick detects Hb and myoglobin.

Management Ensure adequate hydration and urine output. Treatment with sodium bicarbonate has not been shown to ↓ AKI.

Burns

The mechanism of burn is important (e.g. fire, hot water, paraffin, kerosene, electric shock) as may point towards associated problems such as inhalational injury. Electrical burns are often more serious than they appear. Damaged skin and muscle can → AKI.

Management

- Remove source of burning, and cool.
- ABCDE, then determine burn depth and area (Box 19.3).
- Obtain good IV access and give early fluid replacement (Box 19.4).
- Keep burns clean.
- Indications for hospital admission include:
  - >10% burn area in child.
  - >15% burn area in adult.
  - Burns in very young, elderly, or infirm patients.
  - Full-thickness or circumferential burns.
  - Burns with inhalation.
  - Burns of face, hands, feet, perineum.
- Consider possible inhalation injury in patients with facial burns, singed facial or nasal hair, hoarseness, and circumferential full-thickness burns of the chest or neck. If there is inhalation injury, may require early intubation or tracheostomy before laryngeal oedema makes this impossible!
- Look for and treat any associated trauma or pre-burn illness.
- High risk of infection—monitor for signs of sepsis. Early recognition and treatment of 2° infection is essential.
- Routine prophylactic antibiotics are controversial. There are limited data from resource-poor regions, but infection risks likely to be higher in such settings. Base decisions on burn severity, factors such as young age, elderly, nutritional status, HIV status, and the patient's environment.
- Check tetanus immunization status; give tetanus booster if needed.

Box 19.3 Estimating depth and area involved by burns

Depth of burn

- *First degree*: red, pain, no blisters.
- *Second degree*: red or mottled, pain, blisters.
- *Third degree*: dark and leathery, no pain, dry.
  Common to find all three depths within the same burn.

Percentage of body surface area involved

- *Adults*: 'rule of 9s': head 9%, front and back of torso 18% each, arms 9% each, legs 18% each, genitalia 1%.
- *Children*: use palm of child's hand to represent 1% surface area.

Box 19.4 Fluid resuscitation

Adults

Give 2–4mL/kg/% surface area burned in the first 24h (give half in first 8h and half in next 16h).

E.g. an 80kg adult with 25% burns:

Children

Give 4mL/kg/% surface area burned in the first 24h, plus maintenance fluids (➲ Calculating maintenance fluids in children, p. 7). Give half this volume in first 8h and half in next 16h. Suitable fluids are 0.9% saline with 5% glucose, or Ringer's lactate with 5% glucose.

E.g. an 18kg child with 25% burns:

Total fluid in first 24h: (maintenance) + (resuscitation volume)
(56mL × 24h) + 4mL × 18kg × 25 = 1344mL + 1800mL = 3144mL.
Give 1572mL in first 8h and another 1572mL in next 16h.

Further reading

For further information on the management of burns of various depths see:
Papini R. ABC of burns: management of burn injuries of various depths. Br Med J 2004;328:158–60. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC478230/.

Pregnant trauma patients

A similar ABCDE approach should be used for pregnant patients, but anatomical and physiological changes in pregnancy are important.

Anatomical changes

The uterus is vulnerable to damage. In the 1st trimester the fetus is well protected by thick-walled uterus, pelvis, and large amounts of amniotic fluid. By 12wks' gestation the fundus is at the symphysis pubis; by 20wks, at the umbilicus; and by 36wks, at the xiphoid.

Physiological changes in pregnancy

- ↑ tidal volume and respiratory alkalosis.
- ↑ HR; 30% ↑ in cardiac output.
- BP usually 15mmHg lower when lying flat.

Additional risks in pregnancy

Blunt trauma may → uterine irritability and premature labour. Beware of partial/complete uterine rupture; partial/complete placental separation (up to 48h later); and severe blood loss after pelvic fracture.

Management

- Assess mother according to usual ABCDE schema.
- *Resuscitate in left lateral position to avoid aortocaval compression.*
- Perform vaginal examination with a speculum to look for vaginal bleeding and cervical dilatation.
- Mark the fundal height and assess tenderness.
- Monitor the fetal HR.
- Resuscitation of mother may save baby. However, sometimes only option to save mother is to deliver baby by Caesarean section.

Paediatric trauma

Trauma is a leading cause of death in children. Survival depends on early resuscitation. Initial assessment is identical to that of adult, following ABCD, and finally E (exposing child) without losing heat. Blood volume is 80mL/kg in a child, 85–90mL/kg in a neonate.

Physiological reserves of children mean that vital signs may be only slightly abnormal despite up to 25% of blood volume loss. Tachycardia is an early response, and useful for monitoring, but can also be ↑ by fear or pain.

Fluid management

Give 20mL/kg of fluid initially to any child showing signs of class 2 hypovolaemia or worse (Table 19.2), repeated up to 2× (up to 60mL/kg total) depending on the response. Children with little or no response require further fluids and blood transfusion: initially 20mL/kg of whole blood or 10mL/kg of packed RBCs over ~30min.

Heat loss occurs rapidly and a child who is hypothermic may become refractory to treatment. Keep warm.

Acute gastric dilatation (gastroparesis) is common in a seriously ill or injured child. Decompress stomach by inserting an NGT.

Analgesia, e.g. morphine 50 micrograms/kg IV bolus, followed by 10–20 micrograms/kg at 10min intervals until adequate response achieved.

Table 19.2 Classification of hypovolaemia in children

	Class 1	Class 2	Class 3	Class 4
Blood lost	<15%	15–25%	25–40%	>40%
Pulse rate	↑	>150	>150	↑ or ↓
Pulse pressure	↔	↓	↓↓	Absent
Systolic BP	↔	↓	↓↓	Unrecorded
Capillary refill	↔	↑	↑↑	Absent
Respiratory rate	↔	↑	↑	↓, sighing
Mental state	↔	Irritable	Lethargic	Coma
Urine (mL/kg/h)	<1	<1	<1	<1

Poisoning and envenoming

Michael Eddleston

David Warrell

Acute poisoning

Most deaths from acute poisoning are due to deliberate self-poisoning. Although drug poisoning is common in urban areas of resource-poor regions, the majority of deaths occur in rural areas after ingestion of pesticides. While outcome seems to be determined purely by the amount ingested for some pesticides, good management for poisoning by other agents can reduce the death rate.

General management

- *Resuscitate and stabilize* (➔ Life support algorithms, inside covers of this handbook): in particular, take care of the airway, intubating any patient unable to protect their own airway (check the cough and gag are intact).
- *Give high-flow O_2*: except for paraquat-poisoned patients.
- Place patient on their left side to reduce the risk of aspiration and passage of poison; it will also help keep their airway open.
- *If the patient has taken a pesticide*: determine whether he/she needs atropine (➔ Organophosphates/carbamates, p. 818). This can be life-saving.
- Suck out secretions as necessary (however, in organophosphate poisoning, patients will require atropine to control secretions).
- *Get a history*: what has been taken? How much and when? Have a handbook available that lists pesticides by both their chemical class and trade name since many people will only know the latter.
- *Calm the patient*: an agitated poisoned patient makes management difficult and ↑ risk of aspiration; consider diazepam.
- *Watch out for and control convulsions*: first-line therapy is diazepam; second-line for poisoned patients is phenobarbital, not phenytoin (➔ Coma and convulsions, p. 14).
- *Give antidotes according to the poison ingested*: poison identity can come from history or recognition of a 'toxidrome' (Box 20.1).
- Finally, consider value of performing gastric emptying or decontamination once everything else is done.

Gastric lavage and induced vomiting

These are no longer recommended in routine management of the poisoned patient. Studies have shown little return of poison, even when performed in ideal circumstances. Gastric lavage is associated with ↑ ICU admission and ↑ aspiration pneumonia. Only consider within an hour of the poisoning and only if it can be done safely, in a consenting or intubated patient. Gastric lavage performed in a non-consenting struggling patient has a high risk of aspiration and death.

Activated charcoal Administered orally, it offers a large surface area for poison to bind to, ↓ absorption into the body. Give 50–100g (1g/kg for children) dissolved in 200–300mL water.

Multiple doses of activated charcoal Some poisons are excreted in bile or diffuse across the intestinal wall into the lumen. In this situation, repeated administration of activated charcoal every 4h may ↑ elimination.

Osmotic cathartics These are no longer recommended. They ↑ risk of electrolyte abnormalities with no evidence of benefit.

Box 20.1 Toxidromes

Patients are often unable or sometimes unwilling to state which poison they have ingested. Base treatment on clinical signs and locally the most likely poison ingested. Toxidromes are collections of signs that may assist in diagnosis (e.g. cholinergic or anticholinergic syndromes). See Box 20.2 for classification of common pesticides.

Box 20.2 Classification of common pesticides

Insecticides

- *Organophosphates*: poisoning is often serious, requiring treatment with atropine, ventilation, diazepam, and close monitoring.
- *Carbamates*: similar to organophosphates, but acetylcholinesterase (AChE) inhibition is briefer. However, poisoning may still last 2–4d and patients require ventilation. Both organophosphates and carbamates are associated with aspiration.
- *Organochlorines*: e.g. dichlorodiphenyltrichloroethane (DDT), are little used now due to environmental persistence. Major clinical problem is status epilepticus.
- *Pyrethroids*: low toxicity, but may cause anaphylaxis-like features.

Herbicides

- *Chlorophenoxy compounds*: in large overdoses, → ↓ consciousness and rhabdomyolysis → AKI.
- *Paraquat*: no proven treatment is available. Management appears not to alter clinical course.
- *Chloroacetanilides*: in large overdoses → hypotension and coma.
- *Propanil*: → methaemoglobinaemia; few other signs.
- *Glyphosate*: low toxicity unless pesticide and solvent are aspirated.

Rodenticides

- *Aluminium phosphide*: very toxic. Consider giving severely poisoned patients magnesium 1g IV stat, then 1g every 1h for 3h, then 1g every 6h.
- *Zinc phosphide*: generally less toxic. Treat supportively.
- *Coumarin derivatives*: long-acting warfarin-like compounds. Active bleeding requires vitamin K 1mg; patients without bleeding can often be simply monitored via their INR.
- *Thallium*: highly toxic. Banned in many countries.
- *Carbamates*: highly toxic carbamate, aldicarb, is widely used as a rodenticide.

There are many other, often newer, pesticides. None have specific antidotes; conservative management with airway support, close observation and monitoring, and diazepam for seizures is probably best. Some toxicity appears to be due to the solvent in which pesticides are formulated. Aspiration of pesticide and solvent/surfactant co-formulants can cause severe lung injury.

Acute pesticide poisoning

Early careful resuscitation and supportive care of pesticide-poisoned patients, with correct use of antidotes, will ↓ deaths. Most pesticides are dissolved in organic solvents, which can → fatal pneumonia if aspirated; other additives, such as methanol, can → additional toxicity. Beyond 1h, gastric lavage is futile because of a high risk of complications; forced vomiting *should not be performed*. Activated charcoal should be administered orally or by NGT (Box 20.3).

Organophosphates/carbamates See ➲ Organophosphates/carbamates, p. 818.

Organochlorine poisoning Pesticides, e.g. endosulfan, endrin, and less toxic lindane, → status epilepticus after large ingestions.

Management With diazepam; give phenobarbital and then general anaesthetic if no response. Many organochlorines are banned worldwide.

Pyrethroids Synthetic derivatives of the plant-derived pyrethrin. Low toxicity but may cause anaphylaxis-like signs. Manage supportively.

Chlorophenoxy herbicides

Include MCPA; 2,4-D; 2,4,5-T (latter two appear more toxic). Cause coma, oxidative uncoupling, and rhabdomyolysis after large overdose. Observe for black urine (indicates myoglobinuria) and muscle pain.

Management Keep high urine output with IV fluids. Give sodium bicarbonate 3mmol/kg if urine is black. Normally has a good outcome if renal failure averted.

Paraquat

Uniformly fatal if taken in large amounts due to multiorgan failure. Smaller doses may result in fatal lung fibrosis. Patients often have marked ulceration of mouth, since they may just take it into their mouth, then spit it out; oesophageal damage indicates that paraquat was swallowed and is a poor prognostic sign. Early intensive haemofiltration may offer some benefit; there is no evidence that high-dose immunosuppression prevents death.

Management Conservative. Activated charcoal should be given early. Gastric lavage risks oesophageal perforation. O_2 may ↑ lung fibrosis but can be given to ↓ distress.

Propanil Causes methaemoglobinaemia (metHb). Patients look cyanosed, but are asymptomatic if metHb levels are <20%; headaches and low GCS score occur as metHb level rises. Death occurs with metHb >70%.

Management Give methylthioninium chloride (methylene blue) 1–2mg/kg IV over 5min, repeated after 30–60min as necessary, and/or exchange transfusion. Titrate treatment to metHb level.

Glyphosate Causes ulcerative damage to oesophagus, but usually little else. Do not perform lavage since complications may follow aspiration.

See Boxes 20.4 and 20.5 for poisoning with corrosives and hydrocarbons, respectively.

Box 20.3 Gastric lavage for pesticide poisoning

- Lavage must not be performed in combative, conscious patients or in patients with reduced GCS score unless intubated.
- Lavage should only be considered when patients present <1h after ingestion of a potentially life-threatening amount of pesticide (usually organophosphate, organochlorine, or carbamate).
- Use an 18G NGT for pesticides. A larger bore tube has a higher rate of complications.
- Give around 1L of fluid, in 300mL amounts.

Box 20.4 Poisoning with corrosives

After ingestion, acids → an immediate mucosal burn that scabs over, limiting damage. In contrast, alkalis → liquefactive necrosis → much deeper tissue damage.

Clinical features Pain in mouth, throat, and abdomen; dysphagia; drooling. Complications incl. perforation, haemorrhage, and systemic complications of the particular corrosive (e.g. acidosis). Patients with severe poisoning are at high risk of strictures in oesophagus or stomach.

Management Give O_2 and obtain IV access for fluid resuscitation. Watch for signs of airway obstruction or GI perforation. GI decontamination is not indicated. Careful endoscopy is recommended soon after admission to assess damage to GI tract and manage strictures. Patients with alkali ingestions and circumferential oesophageal burns may benefit from early steroids (hydrocortisone 100mg bd), although evidence is weak.

Box 20.5 Poisoning with hydrocarbons

- Hydrocarbon toxicity occurs after pulmonary aspiration or after systemic absorption. The compounds can be grouped by volatility/viscosity and systemic toxicity.
- Poisoning with *non-volatile, non-absorbed* hydrocarbons, such as motor oil does not require treatment. The risk of aspiration is low.
- Poisoning with more *volatile, but non-toxic* hydrocarbons, such as kerosene (paraffin), is very common. Aspiration pneumonia is the main complication so treat conservatively without inducing vomiting or gastric lavage.
- The management of *volatile and toxic* hydrocarbons such as phenol is difficult. Lavage may be indicated in hope of preventing systemic toxicity if the patients have taken a very big dose and been admitted <1h after ingestion. Beware of causing aspiration pneumonia.
- Care for these patients is supportive with very careful protection of the airway. There is no general antidote; steroids are not indicated.

Organophosphates/carbamates

These pesticides inhibit AChE at autonomic, neuromuscular, and central synapses causing acetylcholine (ACh) to accumulate and overstimulate receptors. AChE reactivates quickly in carbamate poisoning; the process is much slower in OP poisoning → more prolonged poisoning. Atropine antagonizes ACh at muscarinic receptors, reversing parasympathetic features. Oximes, such as pralidoxime reactivate inhibited AChE; however, whether oximes benefit patients is unclear.

Clinical features

Result from accumulation of ACh at *muscarinic* synapses (salivation, bronchorrhoea, urination, diarrhoea, bradycardia, small pupils); *nicotinic* synapses (muscle fasciculation, weakness, tachycardia, large pupils); *CNS* synapses (agitation, confusion, drowsiness, coma). Inhibition of AChE over hours to days may → failure of the neuromuscular junction and the intermediate syndrome (initially neck flexion weakness, sometimes cranial nerve palsies, respiratory muscle weakness and sudden respiratory arrest). Some organophosphates → delayed peripheral motor neuropathy after several weeks.

Diagnosis

Diagnosis is normally based on typical clinical features. Plasma butyrylcholinesterase levels may support the diagnosis.

Management

- Resuscitate and support.
- Consider decontamination once the patient is stable.
- Give O_2: intubate early—as soon as patient's GCS score ↓ to <12–13.
- Give diazepam 10mg IV slowly over 2–3min as required.
- Simultaneously, give atropine 1.2–2.4mg rapidly as a bolus. This can be given before O_2 if none is at hand.
- Watch for a response in the markers of atropinization (Box 20.6).
- If no response at 5min, give double the dose of atropine.
- Continue giving doubling doses of atropine until the chest is starting to clear of wheeze or crackles (beware sounds of aspiration) and PR is >80/min. Large amounts of atropine may be required.
- Once patient is atropinized (Box 20.6), set up an infusion giving 20–40%/h of the total bolus dose of atropine required.
- For organophosphates and where agent is unknown, consider give pralidoxime chloride 2g IV slowly over 20–30min (fast injection causes vomiting, tachycardia). An infusion is not currently recommended; repeat qds.
- Treat convulsions with diazepam 10mg IV slowly over 2–3min; repeated as necessary. Intubate and ventilate if required.
- Observe carefully *and regularly* to ensure that (1) the required amount of atropine is being given—↑ or ↓ as required—and (2) detect neck weakness (= early intermediate syndrome; ask patient to lift head off bed against resistance) early so that a patient can be intubated and ventilated before a respiratory arrest. Monitor tidal volume regularly when any weakness is detected.

Box 20.6 Markers

Atropinization

Sufficient atropine has been given when all the following are attained:

- Chest clear (no wheeze or crackles).
- Pulse >80bpm.
- Systolic BP >80mmHg with urine output >0.5mL/kg/h.

Other signs of atropinization not used for titration include:

- Pupils no longer pinpoint (although may take time).
- Axillae (or oral mucosa) are dry.

Notes

- Aspiration may complicate chest criteria. Differentiate between localized crackles of aspiration and generalized crackles/wheeze of organophosphate poisoning.
- The pupils may dilate late—after 30min or so.
- No need to continue to give atropine until HR is 120–140bpm or pupils widely dilated. Aim to reverse poisoning, not to induce atropine toxicity.

Markers of over-atropinization

Too much atropine is being given if:

- Bowel sounds are absent.
- Patient is in urinary retention.
- Patient is confused (not alcohol/withdrawal related).
- Patient is febrile due to atropine.

Atropine-induced fevers These are a particular problem in patients agitated by alcohol withdrawal and in hot environments. They risk causing cardiac arrest.

Agitation Can be ↓ with oral or IV benzodiazepines. ↓ temperature by sponging and using a fan.

Sustained tachycardias of 120–140/bpm Can → MI in patients with alcohol cardiomyopathy or ischaemic disease.

If atropine toxic, stop the infusion for 30 min and then start again at a lower rate. Over time, can wean off atropine in this way.

Acute poisoning with pharmaceuticals/ chemicals

Relatively few pharmaceuticals have specific antidotes. For most patients, management will be supportive. Lavage, forced vomiting, or activated charcoal are unhelpful.

Benzodiazepines

Inhibitory effect on the CNS → drowsiness, slurred speech, ataxia, rarely coma (small pupils/hyporeflexia), or respiratory failure. Most patients can simply be observed in the left lateral position. If respiratory failure (often with newer, short-acting drugs), intubate/ventilate. Severe poisoning can be briefly reversed with flumazenil 0.2mg IV over 15s repeated with doses of 0.1mg at 60s intervals if required, up to max. 1mg. Flumazenil must not be used if other (particularly pro-convulsant) drugs have been co-ingested.

Cardiac glycosides

Either overdose of digoxin medication or ingestion of a natural glycoside (e.g. yellow oleander seeds—*Cascabela thevetia*). Main effects → dysrhythmias and conduction block. Atropine 0.5mg IV for bradycardia is frequently used but is unlikely to prevent severe dysrhythmia. Temporary cardiac pacing can support the patient through third-degree AV heart block, but risks inducing ventricular arrhythmias in an irritable myocardium. Anti-digoxin antibodies, where available/affordable, can reverse DC shock-resistant VF or cardiogenic shock in severe poisoning.

Isoniazid May cause ↓ consciousness, convulsions, coma, respiratory arrest, metabolic acidosis. If severe, give pyridoxine by slow IV injection (quantity equal to the quantity of isoniazid taken; if quantity unknown, give 5g). Can repeat at 5–20min intervals.

Lithium carbonate

Affects CNS, heart, and kidney. Acute lithium poisoning with normal renal function generally requires only supportive care. In patients with poor renal function and severe poisoning, use haemodialysis to remove lithium. Check serum electrolytes 6–12hrly; if hypernatraemia is present, give 5% glucose until plasma Na+ normal. Since most patients will be on chronic lithium therapy and have nephrogenic diabetes insipidus, they will require high fluid maintenance rates. Monitor carefully.

Opiates

Found in analgesics and recreational drugs. Cause respiratory depression, ↓ consciousness, and pinpoint pupils. In opioid-naïve patients, give repeated boluses of naloxone 0.4–2mg IV; try smaller doses (e.g. 40–80 micrograms) in patients who use opioids regularly. If there is a response, set up a naloxone infusion to counter long-acting or sustained-release opioids. Starting dose is 20–50% of the total initial bolus each hour. Reversal of respiratory depression indicates naloxone response; after several minutes RR should be >10/min. If >2mg naloxone is required, review the diagnosis. Has more than one drug been taken?

Paracetamol

For ingestions of >150mg/kg, give acetylcysteine IV (or orally) unless paracetamol blood levels can be measured and shown to be safe. Safest and simplest regimen = 100mg/kg in 200mL of 5% glucose or 0.9% sodium chloride over 2h, followed by 200mg/kg in 1000mL over 10h. Check bloods at 12h and again at 21h ideally. If liver injury or failure develops, continue as it may improve outcome. If acetylcysteine is unavailable, give methionine 2.5g orally repeated 4hrly for a total of four doses. Check liver and kidney function. Closely monitor blood glucose levels, watching for hypoglycaemia. Beware acetylcysteine-induced anaphylactoid reactions—stop the infusion, give antihistamines, and restart after 30min at a slower rate.

Salicylates

Severe aspirin poisoning may → CNS depression, haematemesis, hyperthermia. However, lethal doses may not affect consciousness. Lesser poisoning → GI pain, N&V, tinnitus. A mixed metabolic acidosis/respiratory alkalosis is common. Metabolic acidosis occurs in young children, respiratory alkalosis more commonly in older patients. Give charcoal and correct electrolyte imbalances. If neurological signs, give 50mL of 50% glucose IV; repeat if necessary. Correct any metabolic acidosis—even if there is respiratory compensation—with sodium bicarbonate infusion; patients commonly require K+ supplementation. The goal of bicarbonate treatment is to restore normal systemic pH and alkalinize the urine (urine pH >7).

Tricyclic antidepressants

May → CNS toxicity (convulsions, ophthalmoplegia, muscle twitching, delirium, coma, respiratory depression), anticholinergic effects (dry mouth, blurred vision, mydriasis), cardiotoxicity (QRS duration and QT prolongation), hypothermia, pyrexia. Control convulsions; monitor heart and correct arrhythmias; control acidosis. Give IV sodium bicarbonate for cardiotoxicity or seizures with an initial dose of 3mmol/kg. This dose can be repeated and titrated against clinical response. The pH should be assessed, if possible, after a total dose of 6mmol/kg and should not exceed pH 7.55.

Cyanide

Early signs are altered mental status, tachypnoea (in absence of cyanosis), unexplained anion gap metabolic acidosis, and bright red blood. Late presentations incl. dyspnoea, cyanosis, or unconsciousness. Give O_2; correct acidosis; give amyl nitrite by inhalation over 30s/min until other drugs are prepared. Then give: sodium nitrite 300mg by IV injection over 5–20min followed by sodium thiosulfate 12.5g IV over 10min (alternative: dicobalt edetate 300mg IV over 1min followed by 50mL of 50% glucose. Repeat ×2 if required).

Metal ions (e.g. gold, mercury, zinc, lead, copper)

Acute poisoning can → coma, convulsions, and death, or affect multiple organ systems. Anticipate and treat shock, renal, or hepatic failure. Give penicillamine 1–2g oral od divided into three doses (2h before meals, if possible) for 2–4wks. Get a senior opinion. An alternative option (preferred in mercury poisoning) is dimercaprol (British anti-Lewisite) 2.5–3mg/kg every 4h for 2d; then qds on the 3rd day; and bd for days 4–10 or until recovery.

Mushroom poisoning

Mushrooms cause a variety of toxic effects on the CNS, kidney, liver, muscle, and GI tract. Clinical features are separated into those appearing early (<6h) or late (>6h) after ingestion.

Clinical features

Early symptoms

Start within a few hours: gastroenteritis, cholinergic (muscarinic) effects, confusion, visual hallucinations, or disulfiram-like reactions to drinking alcohol, according to the species ingested.

Delayed symptoms

Starting 6h to many days later suggest more dangerous poisoning:

- Gastroenteritis with hepato- and nephrotoxicity (amatoxin poisoning) is caused by death cap mushroom (*Amanita phalloides*) and others from *Amanita*, *Galerina*, and *Lepiota* genera. Abdominal pain, vomiting, and watery diarrhoea start after 6–24h (usually 12h) → dehydration. Hepatic and renal failure evolve over days to weeks.
- Gastroenteritis with neurological symptoms (gyromitrin poisoning) caused by false morel (*Gyromitra esculenta*). Gastroenteritis, bloating, severe headache, vertigo, pyrexia, sweating, diplopia, nystagmus, ataxia, and cramps followed by delirium, coma, hepatic and renal damage, hypoglycaemia, and haemolysis.
- Renal damage may develop 2–17d after eating *Cortinarius* spp. (orellanine poisoning). Fatigue, intense thirst, headache, chills, paraesthesiae, tinnitus and abdominal, lumbar, and flank pain → polyuria, oliguria, and anuria.
- Rhabdomyolysis occurs after ingestion of *Tricholoma* spp. due to a myotoxin.

Management

- Give activated charcoal 50g every 2h for at least 48h.
- Correct hypovolaemia, acid–base disturbances, hypoglycaemia, and renal failure.
- Give atropine (adult 0.6–1.8mg IV) for cholinergic features.
- Give physostigmine (adult 1–2mg IV) or diazepam (adults 5–10mg IV) for anticholinergic hallucinations.
- For amatoxic fungal poisoning, give silibinin/silybin milk thistle (*Silybum marianum*) extract (bolus dose of 5mg/kg IV over 1h, followed by continuous infusion 20mg/kg/24h for 3d post ingestion). Alternatively, give large doses of benzylpenicillin (2.4g qds). Acetylcysteine and polymyxin B may be beneficial. Liver transplantation may become necessary.
- Gyromitrin poisoning is treated with pyridoxine 25mg/kg over 30min, 5% glucose IV, and diuresis.

Prevention

Discourage the ingestion of any wild fungi, esp. those with white gills. Cooking does not destroy their poisons.

Methanol poisoning

A common form of poisoning globally, resulting from drinking illegal contaminated forms of alcohol → epidemics and many deaths. Diagnosis is very difficult due to the lack of distinctive clinical characteristics and to the lack of laboratories able to measure methanol or its metabolite formate.

Clinical features

Early symptoms incl. intoxication, headache, dizziness, diarrhoea, and vomiting. Delayed features incl. poor/blurred vision, coma, seizures, hyperventilation, and mixed metabolic acidosis/respiratory alkalosis as the formate metabolite is formed.

Diagnosis

Methanol and formate can be measured in the blood. Other markers of poisoning: an early ↑ osmolar gap (before the methanol is metabolized → formate) and a later ↑ anion gap metabolic acidosis (after formate produced).

Management

Prevent the formation of formate so that the methanol can be eliminated by the kidneys. Ethanol and fomepizole inhibit the responsible enzyme, alcohol dehydrogenase.

Ethanol Can be given to maintain a blood ethanol concentration of around 100mg/L. Loading dose of 2.5mL/kg of 40% ethanol (spirits, e.g. whisky, vodka) orally or 10mL/kg of 10% ethanol by IV infusion over 30 min; if unable to measure blood ethanol, maintenance doses are typically from 0.25mL/kg/h (non-drinker or child) to 0.6mL/kg/h (heavy drinker) of 40% ethanol orally; 1–2.5mL/kg/h of 10% ethanol by IV infusion.

Fomepizole This is easier to administer and does not require monitoring. Loading dose: 15mg/kg IV diluted to a final volume of 250–500mL saline or glucose over 30min. Maintenance: 10mg/kg IV diluted to a final volume of 250–500mL saline or glucose over 30min every 12h (starting at 12h after the loading dose is given) for max. four doses; followed by 15mg/kg IV diluted to a final volume of 250–500mL saline or glucose over 30min every 12h thereafter.

Dialysis If neither antidote is available, haemodialysis to remove methanol and its metabolite may be life-saving. ↑ doses of fomepizole will be required during dialysis.

Fish and shellfish poisoning

Ciguatera fish poisoning

Due to accumulation of toxins from the flagellate *Gambierdiscus toxicus* in muscles of carnivorous fish at the top of the food chain. 500,000 cases occur each year. In some Pacific islands >1% are affected/yr, case fatality 0.1%. The polyether toxins activate Na^+ channels. Gastroenteritis develops 1–6h after eating warm-water shore or reef fish (groupers, snappers, parrot fish, mackerel, moray eels, barracudas, jacks). GI symptoms resolve within a few hours, but paraesthesiae (reversed hot–cold sensation), pruritus, and myalgia may persist for days to months. Rare complications incl. cardiotoxicity and respiratory paralysis.

Tetrodotoxin poisoning

Scaleless porcupine, sun, puffer, and toad fish (*Tetraodonitiformes*) become poisonous seasonally. Puffer fish ('fugu') is relished in Japan. Neurotoxic symptoms develop 10–45min after eating the fish and respiratory paralysis may → death 2–6h later.

Scombroid poisoning (histamine-like syndrome)

Histamine is released by bacterial contamination and decomposition of, e.g. dark-fleshed tuna, mackerel, bonito, and skipjack, and of canned fish. Soon after ingestion buccal tingling, stinging or peppery flavour is followed by flushing, burning, sweating, urticaria, pruritus, headache, abdominal colic, nausea, vomiting, diarrhoea, asthma, giddiness, and hypotension.

Paralytic shellfish poisoning

Bivalve molluscs (mussels, clams, oysters, cockles, and scallops) become toxic when there is a 'red tide' of algal blooms. Within 30min of ingestion, paralysis begins and, in 8% of cases → fatal respiratory paralysis within 12h.

Management (of all types of fish/shellfish poisoning)

- Activated charcoal binds some marine toxins.
- Early ciguatera poisoning may respond to IV mannitol.
- Scombroid poisoning responds to antihistamines, bronchodilators, and adrenaline.
- Assisted ventilation is required in severe paralytic poisoning.

Prevention

Marine poisons are not destroyed by cooking or boiling.

- Seek local advice about what is safe to eat.
- Prohibit eating shellfish when there has been a 'red tide' (toxic plankton bloom).
- Prohibit eating very large reef fish (ciguatera poisoning), especially any parts of the fish other than muscle.
- Prohibit eating notorious species, e.g. Moray eels (ciguatera), parrot fish (palytoxin) or puffer fish (tetrodotoxin).

Box 20.7 describes the features, treatment and prevention of leech bites.

Box 20.7 Leech bite

Land leeches infest rainforest floor, attaching to legs or ankles. After a painless bite, they ingest blood, then drop off, but the wound continues to bleed and the clot is fragile. Aquatic leeches are swallowed in river or pond water, or they attack bathers, entering mouth, nostrils, eyes, vulva, vagina, urethra, or anus.

Clinical features

Main effect is blood loss (Fig. 20.1). Other symptoms incl. 2° infection (by symbiotic *Aeromonas hydrophila* even with medicinal leeches), itching, and phobia. Ingested aquatic leeches attach to the pharynx, → sensation of movement at back of throat, cough, hoarseness, stridor, breathlessness, epistaxis, haemoptysis, haematemesis, or upper airway obstruction; or they penetrate bronchi or oesophagus. Via anus, may → rectosigmoid junction → perforation and peritonitis.

Treatment

Apply salt, a flame, alcohol, turpentine, or vinegar to the leech to encourage detachment. Control local bleeding with a styptic, such as silver nitrate, or a firm dressing. Remove penetrating aquatic leeches endoscopically. Spray with 10% tartaric acid or 1:10,000 adrenaline (nasopharynx, larynx, trachea, or oesophagus) or irrigate with concentrated saline (GI tract and rectum).

Prevention

Trousers, socks, and footwear should be impregnated and skin anointed with DEET. Leech-proof socks and gaiters are available. Discourage bathing in or drinking from leech-infested waters. Boil or filter drinking water.

Fig. 20.1 Attached leech and bleeding bite site, Mulu, Sarawak.
Source: Adapted from image courtesy of Dr BE Juel-Jensen.

Snake bite

Venomous snakes → millions of bites and >100,000 deaths/yr (45,000 deaths/yr in India alone). Hot spots are W Africa, S Asia, New Guinea, and Amazon region. Medically important groups are elapids (e.g. cobras, kraits, mambas, coral snakes, Australian snakes), vipers, pit vipers, burrowing asps, and a few species of back-fanged colubrids. Do not be discouraged by all the different species; you need only know about the few dangerous ones where you live and work. See Colour Plates 27–30.

Clinical features (depending on the species involved)

- Local pain, swelling, bruising, blistering, tender regional lymph node enlargement, and tissue necrosis. Occur with vipers, pit vipers, burrowing asps, and some cobras.
- Incoagulable blood, shown by 20min clotting test (Box 20.8), spontaneous bleeding from gums, nose, skin, GI tract, and genitourinary tract; persistent bleeding from wounds. Occurs with vipers, pit vipers, South African boomslang and vine snake, and Australasian elapids.
- Shock (hypotension) and cardiac arrhythmias. Occur with vipers, pit vipers, burrowing asps and Australasian elapids.
- Descending paralysis (ptosis and external ophthalmoplegia, progressing to bulbar and respiratory muscle paralysis, and finally generalized flaccid paralysis). Occurs with elapids, a few vipers and pit vipers.
- Generalized rhabdomyolysis (myalgia, myoglobinuria—black urine that is dipstick +ve for blood). Occurs with sea snakes, some kraits, Australasian elapids, a few vipers, and pit vipers.
- AKI. Occurs with sea snakes, some other elapids, vipers, and pit vipers.

Hospital treatment

First aid—see Box 20.8. Assess and observe all patients carefully for 24h.

- *Antivenom*: only specific antidote is indicated for any signs of systemic envenoming listed on ➔ Clinical features, p. 827, *or* for local envenoming that is rapidly spreading *or* involves more than half the bitten limb or digits within 24h. Give an appropriate antivenom (check package insert for species covered) by slow IV injection or infusion.
- Give prophylactic SC adrenaline (0.1%; adult 0.25mg, child 5 micrograms/kg). Watch for early signs of anaphylactic reactions and treat immediately with IM adrenaline (adult 0.5mg, child 10 micrograms/kg) and IV H1 antihistamine and hydrocortisone 200mg. Do not do potentially sensitizing, time-wasting, non-predictive hypersensitivity tests.
- Give tetanus toxoid booster to all snake bite cases, envenomed or not.
- Give antibiotics (penicillin/erythromycin with aminoglycoside, or chloramphenicol) if local necrosis, interference with, or contamination of bite site, or abscess formation.
- Intubate/ventilate if bulbar/respiratory paralysis.
- Correct hypovolaemia (extravasation/bleeding into swollen limbs).
- Treat AKI with renal replacement therapy.
- Nurse swollen limbs in the most comfortable position.
- Debride necrotic tissue, but avoid fasciotomy unless intracompartmental pressure is consistently >40mmHg and only after haemostasis has been restored.

Box 20.8 Snake bite prevention and treatment

First aid

- Reassure patient (only ~50% of bites by venomous snakes cause envenoming, which usually takes hours to become serious).
- Do not interfere with bite site in any way (e.g. do not attempt to suck out or aspirate venom).
- Immobilize person as far as possible, esp. the bitten limb.
- Apply pressure-pad over wound with splint immobilization (Figs. 20.2 and 20.3).
- Transport patient to medical care by vehicle, boat, stretcher, etc., avoiding shock, aspiration, and respiratory obstruction/failure en route.
- Treat pain with paracetamol or codeine (not for children); avoid aspirin or NSAIDs.
- Never attempt to catch or kill the snake.
- Never use traditional methods (tourniquet, incision, suction, herbs, electric shock, etc.).

20min whole-blood clotting test

Put 2mL of venous blood into a new, plain glass—not plastic—test tube. Leave undisturbed for 20min, then tip once. If blood runs out (no clot), consumption coagulopathy has occurred and antivenom is indicated. Repeat 6h after giving antivenom. If blood remains incoagulable, give another dose. If the blood clots initially, the test can be repeated hourly if envenoming is suspected. Recovery will take 6h after effective administration of antivenom since the liver must restore coagulable levels of clotting factors.

Pressure-immobilization methods

Elapid venoms can → rapid paralysis. Unless an elapid bite can confidently be excluded, firmly apply ~6 × 6 × 3cm pad of material immediately over the bite wound, using a non-elastic bandage, and immobilize the limb with a splint (Fig. 20.2). Alternatively, bind whole bitten limb firmly with long elasticated bandages, from digits to axilla/groin, incorporating a splint (Fig. 20.3). Loosen if limb becomes painful/cold and blue, or if peripheral pulses are impalpable.

Prevention of snake bites

- Avoid all snakes and snake charmers.
- Never disturb, corner, attack, or handle snakes, dead or alive.
- If a snake is cornered, remain motionless until it has escaped.
- Never walk in undergrowth or deep sand without proper leg/footwear.
- Always carry a light and stick at night.
- Be careful collecting firewood with bare hands.
- Never put a hand or push sticks into burrows or holes.
- Avoid climbing trees or rocks covered with dense foliage.
- When climbing, do not put hands on ledges that cannot be seen.
- Never swim in vegetation-matted rivers or muddy estuaries.
- Avoid sleeping on the ground—use a hammock or camp bed, a tent with sewn-in ground sheet, or a mosquito net well tucked-in under the sleeping bag.

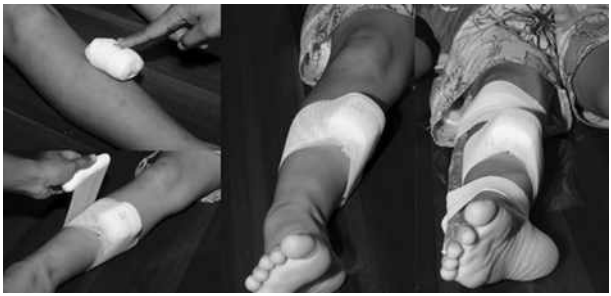

Fig. 20.2 Pressure pad immobilization method. A pad of rubber or cloth approx. 6 × 6 × 3cm is applied directly over bite site, secured tightly with inelastic bandage at ~70mmHg pressure. The bitten limb is splinted.

Source: Image courtesy of Dr David J Williams.

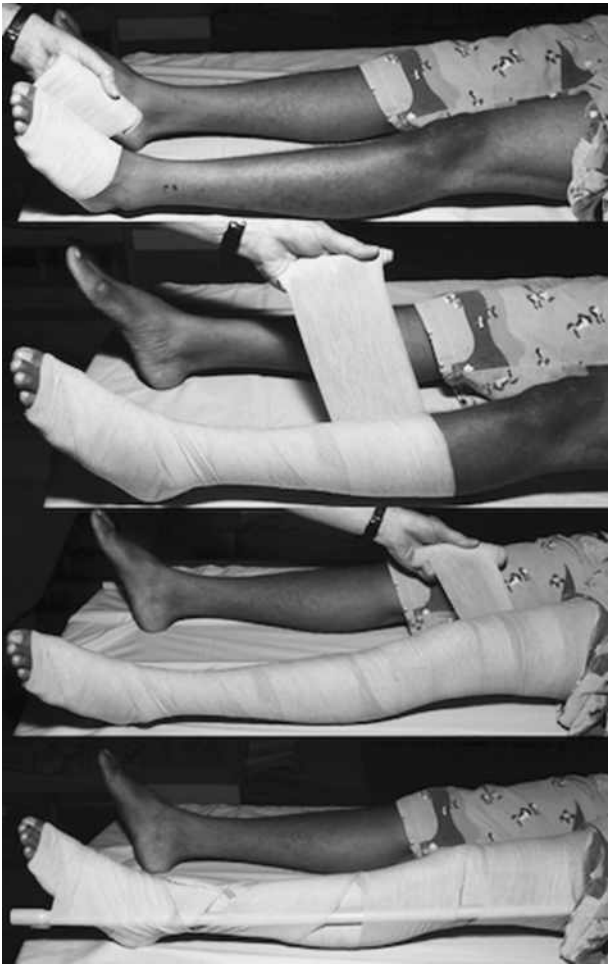

Fig. 20.3 Compression-bandage immobilization method. Use 3× elastic (not crepe) bandages 10 cm wide × 3.5–4.5m long. The bitten limb is splinted. For upper limb bites, bind and splint with the arm extended at the elbow.

Source: Image courtesy of Dr David J Williams.

Scorpion sting

The most dangerous scorpions (Fig. 20.4) inhabit deserts or hot dusty terrain in N Africa, Middle East, S Africa, the Americas, and S Asia. They probably cause >1 million stings/yr, and >3000 deaths (mostly in children)/yr (Fig. 20.5).

Clinical features

Stings are excruciatingly painful (Fig. 20.5). Systemic symptoms reflect release of autonomic neurotransmitters: ACh (→ vomiting, abdominal pain, bradycardia, sweating, salivation) and then catecholamines (→ hypertension, tachycardia, pulmonary oedema, and ECG abnormalities).

Management

For pain, infiltrate local anaesthetic at the site, using digital block if the sting is on a digit. Powerful opiate analgesia may be required. For systemic envenoming (difficult to distinguish from pain and fear in children), antivenoms are available for dangerous African/Middle Eastern, Indian, and American species. Hypertension, acute LVF, and pulmonary oedema may respond to vasodilators such as prazosin (0.5mg oral every 3–6h), and hypotension to dobutamine.

Prevention

Scorpions hide in cracks, crevices, and under rubbish. Encourage people to not walk around in bare feet, to sleep off the ground under a permethrin-impregnated bed net, and always to shake out boots and shoes before putting them on.

Fig. 20.4 Granulated thick-tailed scorpion (*Parabuthus granulatus*) from South Africa: a large (adults ~12cm long) brown-coloured scorpion; its venom is extremely potent and causes respiratory paralysis.

Source: Image courtesy of D A Warrell.

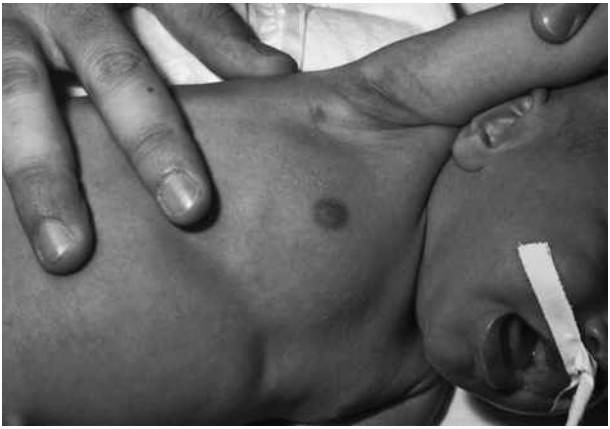

Fig. 20.5 Site of Brazilian yellow scorpion (*Tityus serrulatus*) sting on the axilla of a 26d-old child in São Paulo, Brazil.
Source: Image courtesy of D A Warrell.

Spider bite

The most dangerous spiders are:

- Black/brown widows (*Latrodectus*) in the Americas, southern Europe, southern Africa, Australia and elsewhere.
- Brown recluse spiders (*Loxosceles*; Figs. 20.6 and 20.7) in the Americas, Europe and elsewhere.
- Wandering, armed, or banana spiders (*Phoneutria*; Fig. 20.7) in Latin America.
- Funnel web spiders (*Atrax* and *Hadronyche*) in Australia.

Spiders cause few deaths.

Clinical features

Bites happen when people brush against spiders that have crept into clothes, bedding, curtains etc. *Latrodectus*, *Phoneutria* (Fig. 20.7) and *Atrax* are neurotoxic causing cramping abdominal pains, muscle spasms, weakness, sweating, salivation, gooseflesh, fever, nausea, vomiting, alterations in pulse rate and BP, and convulsions. *Loxosceles* is necrotic (Fig. 20.8). Rarely, *Loxosceles* cause systemic effects such as fever, scarlatiniform rash, haemoglobinuria, coagulopathy, and AKI.

Management Mostly symptomatic. Antivenoms available in S Africa, Australia, and Brazil where bites are an important medical problem.

See Box 20.9 for anaphylaxis of Hymenoptera stings.

Box 20.9 Hymenoptera sting anaphylaxis

Stings by bees (*Apidae*), wasps, hornets, and yellow jackets (*Vespidae*), and ants (American fire ants *Solenopsis*, Australian jumper ants *Myrmecia*) are a very common nuisance in most countries. However, 2–4% of the population becomes allergic, developing massive local swelling or potentially lethal anaphylaxis if stung a second/subsequent time. Mass attacks by bees and wasp-like insects can occur. In the Americas, Africanized 'killer' bees have killed many people by direct envenoming rather than hypersensitivity.

Clinical features

Symptoms of anaphylaxis including urticaria, angio-oedema, shock, bronchospasm, and GI symptoms.

Management

Give adrenaline IM urgently.

Prevention

Desensitization is effective but time-consuming. Self-injectable adrenaline is the best first aid.

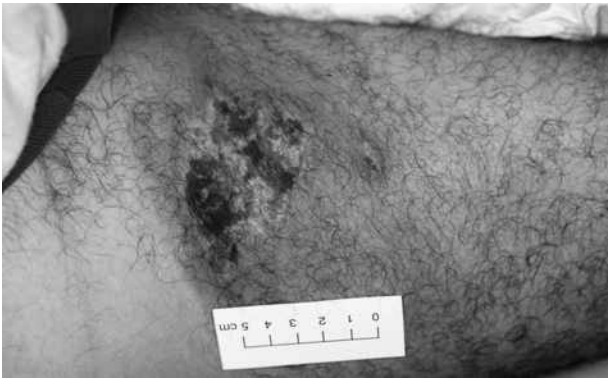

Fig. 20.6 Site of bite by a recluse spider 'Aranha-marrom' (*Loxosceles gaucho*) bite in a 51yr-old man in São Paulo, Brazil, showing, 3d post bite, features of the 'red, white, and blue' sign.

Source: Image courtesy of D A Warrell.

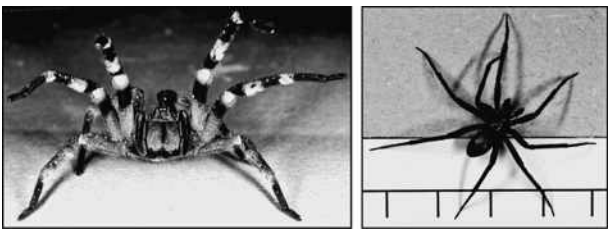

Fig. 20.7 Left: Brazilian wandering or armed spider (*Phoneutria nigriventer*) from São Paulo: 3–5cm in body length with a leg span of 13–15cm. Bite causes neurotoxic araneism—autonomic symptoms. Sometimes exported in bunches of bananas and has caused bites in western countries. Right: Chilean brown recluse spider (*Loxosceles laeta*) specimen from Brazil: small peri-domestic spiders (see centimetre scale in picture; leg span ~4cm) whose bites can cause extensive local necrosis and, sometimes, life-threatening systemic symptoms.

Source: Image courtesy of D A Warrell.

Fish stings

Stinging fresh- and saltwater fish (stingrays, cat fish, weevers, scorpion fish, stone fish (Fig. 20.8), etc.) have venomous spines on gills, fins, or tail. Most commonly, they sting when trodden upon on the ocean or river bed.

Clinical features

Immediate excruciating pain, → local swelling and inflammation. Rare systemic effects incl. vomiting, diarrhoea, sweating, cardiac dysrhythmia, hypotension, and muscle spasms. Stingrays' barbed spines can inflict fatal trauma (pneumothorax, penetration of organs). Spines embedded in wound with their venomous integument will → infection.

Management

First aid Agonizing local pain is dramatically ↓ by immersing stung part in hot but not scalding water. Local anaesthetic can also be infiltrated or applied as digital block for pain relief.

Antivenom Australia produces an antivenom for the most dangerous species—stone fish (genus *Synanceia*; Fig. 20.8).

Infection All fish wounds can become infected with lethal aquatic bacteria (salt water *Vibrio vulnificus*, fresh water *Aeromonas hydrophila*); give doxycycline or co-trimoxazole.

Prevention Advise people to shuffle or prod sand ahead of them with a stick to disturb ground-lurking fish, to avoid handling dead or live fish, and to keep clear of fish in the water, especially in vicinity of tropical reefs. Footwear protects against most species except stingrays.

Fig. 20.8 Estuarine stonefish (*Synanceia horrida*), Cairns, Australia.
Source: Image courtesy of D A Warrell.

Jelly fish stings

Common stinging jelly fish (cnidarians/coelenterates) include: Portuguese men o'war (blue bottles), sea wasps, box jellies, cubomedusoids, sea anemones, and stinging corals. Tentacles are studded with millions of stinging capsules (nematocysts) that fire venomous stinging hairs into skin on contact → lines of painful blisters and inflammation. Allergy may → recurrent urticarial rashes over many months. The notorious Northern Australian and Indo-Pacific box jellyfish (*Chironex fleckeri* and *Chiropsalmus* spp.) and Irukandji (*Carukia barnesi*) can kill. Common sea bathers' eruption is an itchy papular rash underneath the bathing suit, caused by tiny thimble jelly fish.

Clinical features Severe musculoskeletal pain, anxiety, trembling, headache, piloerection, sweating, tachycardia, hypertension, and pulmonary oedema may evolve; or anaphylaxis in those sensitized by previous stings.

Management

Remove victim from water (to prevent drowning). Inhibit nematocyst discharge by applying commercial vinegar or 3–10% aqueous acetic acid (only *Chironex* spp. and other cubozoans including Irukandji) or a slurry of baking soda and water (50% w/v) (*Chrysaora* spp.—Fig. 20.9). Do not use sun tan lotion or alcoholic solutions. Immersion in hot water (➲ Fish stings, p. 835) relieves pain. Adrenaline for anaphylaxis. Antivenom for *Chironex fleckeri* is available in Australia. For minor rashes, use oral antihistamines and topical steroids.

Box 20.10 describes the management of sea urchin stings.

Box 20.10 Sea urchin stings

Long, sharp, venomous sea urchin (echinoderm) spines become deeply embedded in skin, usually of sole of foot, when animal is trodden upon, leaving black/blue stained lesions.

Management

Immersion in hot water (➲ Fish stings, p. 835) relieves pain. Soften skin with salicylic acid ointment and then pare down the epidermis to a depth at which spines can be removed with forceps. Most sea urchin spines are absorbed rapidly provided they are broken into small pieces in skin. If they penetrate a joint or become infected, surgical removal may be necessary.

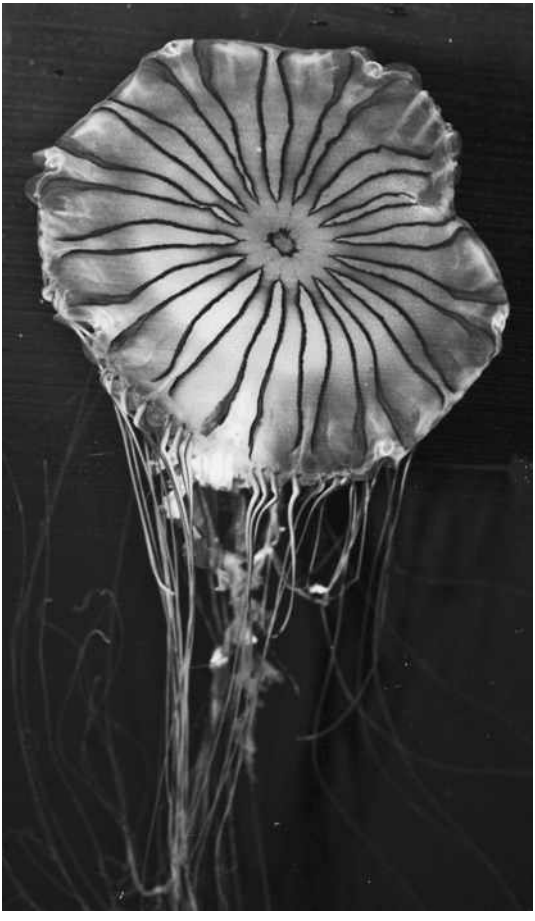

Fig. 20.9 Japanese sea nettle (*Chrysaora pacifica*). Image courtesy of D A Warrell.

Chapter 21

Immunization

Eleonora Mutsaerts

Shabir A. Madhi

Introduction

Vaccines (Box 21.1) continue to be life-saving interventions in LMICs, preventing ~2.5 million deaths annually. Although >100 million children are immunized each year, 14% remain un- or under-immunized: 60% of these children are from Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Iraq, Nigeria, Pakistan, and South Africa. ~1.5 million additional childhood deaths could be averted annually if >90% of children were immunized.

A cold chain and IM injection mean logistic difficulties. Recently licensed vaccines, e.g. rotavirus vaccine and pneumococcal conjugate vaccine, are unaffordable to most LMIC governments. GAVI, the Vaccine Alliance (formerly Global Alliance for Vaccines and Immunisation) provides support to low-income countries to support the introduction and use of vaccines.

National public immunization programmes (Expanded Programme on Immunization (EPI))

See Tables 21.2 and 21.3. The epidemiology of diseases that EPI combats differs among countries, thus immunization policy varies; national policies take precedence over EPI guidelines. See ➔ Figs. 21.1 and 21.2, p. 859, for sites for injection. A summary is available at: https://apps.who.int/immunization_monitoring/globalsummary/schedules.

In addition to EPI, immunization of pregnant women protects their young infants against tetanus, influenza, and pertussis. Group B *Streptococcus* conjugate vaccine and respiratory syncytial virus vaccine are being developed for immunization of pregnant women.

Funding initiatives

GAVI is an alliance between stakeholders e.g. developing and donor governments, the World Bank, WHO, UNICEF, the pharmaceutical industry, research institutes, NGOs, and the Bill and Melinda Gates Foundation, and has brought focus and unprecedented resources to the goal of optimizing immunization uptake and development of new vaccines. Challenges remain in the sustainability of funding, esp. for countries that have progressed economically.

Further reading

WHO. Immunization planning and financing. Available at: https://www.who.int/immunization/programmes_systems/financing/analyses/00_briefcase_En.pdf?ua=1.

Box 21.1 Abbreviations used for vaccines

- *BCG*: Bacille Calmette–Guérin vaccine.
- *BOPV*: bivalent oral polio vaccine.
- *DT*: combination diphtheria toxoid and tetanus toxoid vaccine for use in children <7yrs.
- *DTP*: combination diphtheria toxoid, tetanus toxoid, and pertussis vaccine.
- *DTaP*: combination diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine.
- *DTwP*: combination diphtheria toxoid, tetanus toxoid, and whole-cell pertussis vaccine.
- *DTP-CV*: DTP-containing vaccine.
- *HepB*: hepatitis B vaccine.
- *Hib*: *Haemophilus influenzae* type b conjugate vaccine.
- *HPV*: human papillomavirus vaccine.
- *MMR*: combination measles, mumps, and rubella vaccine.
- *MR*: combination measles and rubella vaccine.
- *IPV*: inactivated (injected) trivalent polio vaccine (Salk vaccine).
- *OPV*: oral polio vaccine (Sabin vaccine).
- *PCV*: pneumococcal conjugate vaccine.
- *Rota*: rotavirus vaccines.
- *Td*: combination tetanus toxoid and low-dose diphtheria toxoid vaccine for use in individuals ≥4yrs.
- *TetT*: tetanus toxoid vaccine.

Table 21.1 Expanded Programme on Immunization

Age[1]	Vaccines	Scheme I[2]	Scheme II
Birth	BCG[3], OPV-04	HepB-1	HepB-1
6wks	DTP-1[5], OPV-1, Hib-1, PCV-1[6], Rota	HepB-2	HepB-2
10wks	DTP-2, OPV-2, Hib-2, PCV-2, Rota		HepB-3
14wks	DTP-3, OPV-3, Hib-3, PCV-3, Rota[7]	HepB-3	HepB-4
9mths	Measles-1[8], Rubella +/−, Yellow fever[9]		
9–18mths	MenA conjugate vaccine[10]		
9–14yrs	HPV-1, -2[11] (females)		
Variable	Japanese encephalitis[12] Tick-borne encephalitis		

[1] Babies born prematurely should be vaccinated at the same times after birth as babies born at term.

[2] The monovalent HepB vaccine is recommended at birth; subsequent immunization can be with either a monovalent vaccine or in combination with diphtheria toxoid, tetanus toxoid and pertussis vaccine (DTP) +/− Hib. While three doses of HepB are considered sufficient (Scheme I), a four-dose schedule (Scheme II) can be used, e.g. if HepB in combination with DTP +/− Hib.

[3] In countries with a high burden of TB or leprosy.

[4] In polio-endemic countries, at ≥1 dose of IPV with DTP-containing vaccine (DTPCV). Since 2016, only bivalent OPV (type 1 and 3) is used.

[5] Countries using whole-cell pertussis-containing vaccines are encouraged not to transition to acellular pertussis vaccine due to ↑ mucosal immunity and ↑ duration of protection.

[6] PCV recommended either as three-dose 1° series (6, 10, or 14wks) or as a two-dose 1° series (ideally at 6 and 14wks) and a booster at 9–15mths. It is likely that a 2+1 dose schedule induces better herd immunity than a 3+0 schedule; HIV-infected children need a booster dose.

[7] Rotarix™: two doses required; RotaTeq™: three doses required. Similar efficacy against severe rotavirus disease. WHO advises that rotavirus vaccines can be administered with DTP vaccine up until 2yrs of age.

[8] Measles vaccination should be initiated at 6mths where there is ↑ risk of mortality from measles <9mths or a high prevalence of maternal HIV-infection. WHO recommends that countries work toward measles–rubella combination vaccine by 2020.

[9] Limited to countries where yellow fever (YF) poses a risk (➲ Yellow fever, p. 761).

[10] A one-dose schedule of MenA conjugate vaccine (5 micrograms) is recommended at 9–18mths.

[11] Two-dose schedule with a 6mth interval between doses.

[12] In endemic countries; variable schedules from 9mths (➲ Japanese encephalitis vaccines, p. 854).

Updates and further details are available at the WHO website: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/ who-recommendations-for-routine-immunization---summary-tables.

Table 21.2 Booster doses

Vaccine	Recommended boosting schedule
Tetanus[1,2]	Further doses to be given at: 12–23mths (DTP-containing vaccine) 4–7yrs age (Td) 9–15yrs age (Td)
Pertussis	12–23mths (DTPCV)
Measles	15–18mths
PCV[3]	9–15mths

[1] Maternal immunization is a highly effective method of controlling neonatal tetanus. Recommendations vary according to previous immunization status.

[2] EPI for children has five doses of tetanus-toxoid vaccine, but a dose in early adulthood is recommended for long-term protection. For children <7yrs of age, DTwP or DTaP combinations may be used. For children aged ≥4yrs, Td is preferred. If acellular pertussis-containing vaccines are used in the 1° series, give booster doses of dTap every 5–7yrs in adolescents.

[3] If using a two-dose 1° series, give a booster dose of PCV at 9–15mths.

Immunization strategies and schedules

Immunization schedule design

Timing of vaccines aim to balance between:

- Desire to immunize as early as possible to protect infants during early infancy when they are vulnerable and before exposure to the infectious agent; and
- Optimizing immunogenicity of vaccines by immunizing when the infant's immune system has matured.
- Minimizing transplacental maternal antibody interference with immune response to vaccine. This effect varies between vaccines.

Many vaccines require >1 dose, which should be separated by ≥4wks. ↑ intervals between doses → ↑ immune response, but could → the child being susceptible to the disease between doses. For some vaccines such as PCV, when using a two-dose 1° series (with a third as a booster dose), it is important to space the 1° doses >8wks apart → similar immune response compared to a three-dose 1° series with dosing 4wks apart. Changes in population immunity require local adaptations.

Optimization of vaccine uptake

A common reason for children dying is that they have not received the full series of recommended vaccines. ↑ vaccine uptake by:

- Offering immunizations whenever under-immunized children attend health facilities.
- Administering all vaccines for which a child is eligible at one visit.
- Routine screening of immunization status of all women and children during contacts with health facilities.
- Awareness of true and false contraindications for immunizations (➲ Contraindications to vaccination, p. 846).
- Appropriate utilization of multidose vials (➲ Transport and storage of vaccines, p. 844).

Transport and storage of vaccines

Most EPI vaccines need a 'cold chain' of optimum temperatures from manufacture to point of use. The following have been introduced:

- *Cold chain monitor*: detects excessive temperatures during shipment.
- *Vaccine vial monitor* (VVM): for the cumulative heat exposure of an individual vial.
- The 'shake test' to detect the effects of freezing on vaccines.
- *Freeze watch™ monitor*: for exposure of vaccine shipments to temperatures below freezing point.
- *Stop!Watch™*: combining the indicators from the cold chain monitor and the Freeze watch™ monitor.
- Off-grid vaccine storage solutions, solar refrigerators, remote alarm systems for vaccine storage.
- *Controlled temperature chain* (CTC): allowing vaccines to be kept at temperatures outside +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen (only in a campaign or special strategy setting).

Guidance is available at: https://www.who.int/publications/i/item/module-1-cold-chain-vaccines-and-safe-injection-equipment-management.

To ↓ vaccine wastage, use already-opened multidose vials at subsequent immunization sessions for BOPV, DTP, TetT, DT, HepB and liquid formulations of Hib. Opened vials can be used for up to 4wks if:

- Cold chain has been maintained, the VVM has not reached the 'discard point', and vaccines are within date.
- The rubber vaccine vial stopper has not been under water (e.g. melting ice).
- Aseptic technique has been used.

For further details, see: https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/supply-chain.

Needle use and disposal

>1 billion vaccines are injected in LMICs annually. Each injection has the potential to transmit blood-borne infections to both vaccinees (through re-use of needles) and HCWs (through needlestick injuries). To ↓ risks:

- Use single use autodestruct needles.
- Use safety boxes to dispose of used needles. Safety boxes should be sealed when ¾ full. Disposal of safety boxes is usually by incineration.
- Disposable syringes must not be recapped.

Adverse reactions

Some vaccines may → adverse reactions. Accurate data on 'Adverse Events After Immunization' has been aided by, e.g. EU Vaccine Adverse Event Surveillance and Communication network and WHO Global Advisory Committee on Vaccine Safety. Adverse event monitoring/reporting is poor in LMICs.

Adverse reactions may be caused by

- *Inappropriate administration*: e.g. abscesses from non-sterile needles/syringes; disseminated BCG or measles in immunocompromised patients.
- *Properties of the vaccines*: e.g. reactions to either the immunizing agent or other components, e.g. antibiotics, adjuvants, preservatives.
- *The immune response to the vaccine*: e.g. allergic reactions.

Mild adverse events

These are common (20–50% of DTwP recipients experience mild local reactions, 5–15% of measles vaccine recipients experience fever and 2% a transient rash 7–12d after immunization). These are not contraindications to further immunization. Although DTaP is less reactogenic than DTwP, DTaP has ↓ duration of protection (5yrs vs 10–12yrs) and does not confer mucosal protection or prevent transmission.

Severe adverse reactions

These are extremely rare. Despite concerns that DTwP causes many adverse events, comprehensive studies have failed to confirm this. Reactions e.g. febrile convulsions or anaphylaxis rarely occur, and vaccine-associated adverse events are much less common than the complications of diseases prevented by vaccines.

Misconceptions about vaccines

There have always been concerns about the safety of immunization. This is understandable because a biologically active agent is given to healthy children. Unfortunately, even after a vaccine's safety has been demonstrated, some beliefs may persist, e.g. the erroneous suggestion of a link between MMR and autism. Recent examples include rumours that OPV → infertility or → spread of HIV. Rumours about adverse events following HPV vaccination and fear of unknown side effects → lower vaccine uptake. Effective education and communication are needed.

Contraindications to vaccination

There are few absolute contraindications; every opportunity to vaccinate a child or woman of child-bearing age should be taken. Delaying vaccination until children recover from mild intercurrent illness may → under-immunized children.

True contraindications to immunization

- If a sick child is hospitalized and is then vaccinated, but dies from another illness the vaccine may be erroneously blamed for the child's death. Immunize as soon as the child's condition improves.
- For live vaccines (➲ Box 21.3, p. 846), immunodeficiency, e.g. malignant disease, immunosuppressive drugs, or irradiation. HIV/AIDS is a special case—see ➲ Immunization of HIV-infected persons, p. 847.
- A severe adverse event (anaphylaxis, collapse or shock, encephalitis, encephalopathy, or non-febrile convulsions) to a vaccine contraindicates further doses of that vaccine. If the adverse reaction occurred following a dose of DTP vaccine, either omit the pertussis component and continue with the DT vaccine or use a vaccine containing acellular pertussis.
- For vaccines prepared in egg (e.g. influenza, YF) a history of anaphylaxis following egg ingestion. Vaccines prepared in chicken fibroblast cells (e.g. measles, MR, MMR) are safe for such individuals.

Live vaccines should generally be avoided in pregnant women, and pregnancy should be avoided for >1mth following immunization with live vaccines. Sometimes the need for vaccination outweighs the possible risk to the fetus (e.g. YF vaccine and BOPV during outbreaks).

Box 21.3 Conditions which are not contraindications and must not prevent a child from being vaccinated

- Minor illnesses e.g. URTI or diarrhoea, with fever <38.5°C.
- Allergy, atopy, asthma, hay fever, or 'snuffles'.
- Prematurity, small-for-dates infants, or neonatal jaundice.
- Malnourished or breastfed child.
- Family history of convulsions.
- Treatment with antibiotics, limited corticosteroid treatment (i.e. prednisolone 2mg/kg/d for <1wk, or 1mg/kg/d for <1mth or equivalent doses of other steroids) or locally acting (e.g. topical or inhaled) steroids.
- Rashes, eczema, or localized skin infection.
- Chronic diseases of heart, lung, kidney, and liver.
- Stable neurological conditions, e.g. cerebral palsy/Down's syndrome.

Immunization of HIV-infected and HIV-exposed-uninfected children

Immunization of HIV-infected (HIV+ve) children needs special consideration because of:

- ↑ susceptibility to severe illness (e.g. from TB, pneumococcal disease, measles).
- ↓ immunogenicity of vaccines administered in advanced HIV infection. Most HIV+ve adults and children mount a moderate or good vaccine response.
- For some vaccines, there might be waning of immunity and ↓ protection over time, → booster doses of vaccines, esp. if the children were not on ART.
- HIV-exposed-uninfected children and HIV+ve children who are vaccinated when already on ART have normal immune responses to most vaccines.
- Potential risk of live vaccines (e.g. disseminated BCG infection following administration of BCG vaccine).
- HIV+ve children should start ART irrespective of CD4 count immediately upon diagnosis, which ↑ survival and → ↑ immune responses to vaccines.

Apart from BCG, asymptomatic HIV+ve individuals should receive all recommended EPI vaccinations at usual ages. The recommendations for children with symptomatic HIV infection are outlined in Table 21.3. Severely ill HIV+ve children should not be vaccinated.

Table 21.3 WHO/UNICEF recommendations for the immunization of HIV-infected children

Vaccine	Asymptomatic HIV infection	Symptomatic HIV infection
BCG	No1	No[1]
DTP	Yes	Yes
BOPV[2]	Yes	Yes
Measles[3]	Yes	Yes[4]
Hepatitis B	Yes	Yes
Hib	Yes	Yes
PCV	Yes	Yes
Rotavirus	Yes	Yes[5]
Yellow fever	Yes	No
TetT	Yes	Yes

[1] If HIV+ve individuals, including children, are receiving ART, are clinically well, and immunologically stable, they should be vaccinated with BCG. Neonates born to women of unknown HIV status should be vaccinated as the BCG benefits > risks. Neonates of unknown HIV status born to HIV+ve women should be vaccinated if they have no clinical evidence of HIV infection. For neonates confirmed HIV+ve, delay BCG vaccination until ART has been started and CD4 >25%.

[2] IPV can be used as an alternative in symptomatic HIV+ve children.

[3] Because of the risk of severe early measles infection and low maternal antibody levels in newborns of HIV+ve women, all HIV-exposed infants should receive measles immunization at 6mths followed by two routine doses, provided there is a high incidence of HIV infection and measles remains endemic.

[4] Consider measles immunization in symptomatic HIV+ve children if not severely immunosuppressed.

[5] Assess potential benefits and risk on individual basis.

Box 21.2 Live attenuated vaccines

- BCG.
- Measles.
- Mumps.
- Rotavirus.
- Rubella.
- MR.
- MMR.
- Varicella.
- BOPV.
- YF.
- Oral typhoid.

Expanded Programme on Immunization recommended vaccines

See ➔ Contraindications to vaccination, p. 846, for general contraindications.

BCG

A freeze-dried preparation of a live attenuated strain of *Mycobacterium bovis* given as a single intradermal injection.

- Different BCG strains exist.
- Early administration is recommended; BCG is most effective in preventing disseminated TB, incl. TB meningitis in children.
- Duration of protection >10–15yrs is uncertain; booster doses are not recommended.
- If BCG is given after the neonatal period, ensure a −ve tuberculin skin test before giving BCG.
- BCG also protects against leprosy.

Contraindications Symptomatic HIV+ve, ART naïve, CD4% ≤25% or other immunocompromised individuals.

Side effects A small swelling forms 2–6wks post vaccination that may → a benign ulcer. Local abscesses may occur, esp. after SC rather than intradermal administration. Regional lymphadenitis occurs in ~0.5%. Most adverse events are self-limiting but isoniazid can be used to treat local infections.

Poliomyelitis vaccine

The Americas, Pacific region, and Europe have been declared polio free. Wild type polio virus type-2 has not been detected since 1999. Only Afghanistan and Pakistan reported endemic polio in 2015—a total of 73 cases were detected.

- Both oral, live attenuated vaccines (OPV, Sabin vaccine) and injectable, killed virus vaccines (IPV, Salk vaccine) are available.
- In 2016, type-2 polio virus was removed from OPV, which now only includes type-1 and type-3 virus (BOPV).
- EPI recommends 3–4 doses of BOPV and ≥1 dose of IPV. BOPV has advantages of low cost, ease of administration, superior intestinal mucosal immunity and shed virus may boost immunity in household and community contacts.
- BOPV vaccine is generally used; however monovalent vaccines against strains 1 and 3 are used in mass immunization campaigns.
- Vaccine-associated paralytic poliomyelitis occurs in ~1 in 250,000 doses of OPV; many countries in 'polio-free' regions have therefore switched to IPV and this trend may continue as the goal of global eradication is reached.

Cautions Patients with diarrhoea and vomiting require a further dose after recovery. IPV rather than OPV should be administered to immunocompromised individuals and their household contacts.

Hepatitis B vaccines

Use a suspension of inactivated HBsAg adsorbed onto alum; given by IM injection at birth and in infancy (➲ Administration of vaccines, p. 859).

- Booster doses are not recommended after 1° course.
- Recombinant and plasma-derived products are equally safe and effective.
- The vaccine is available either as monovalent HepB or in combination with DTP +/− HibCV or DTaP +/− HibCV; only the monovalent vaccine should be used for immunization at birth. New hexavalent formulations which include aP rather than wP, also include IPV.
- Neonatal vaccination provides partial immunoprophylaxis against perinatal infection. Perinatal transmission can be further reduced by giving HepB immunoglobulin at birth, however, there are supply and cost constraints.
- Premature and LBW (<2000g) infants should be vaccinated at birth and also receive three additional doses in infancy.
- Vaccination is safe in pregnancy, lactation, and HIV+ve individuals.
- Following exposure beyond the perinatal period (e.g. after a needlestick injury in unimmunized health workers), a 0, 1, 2mths schedule should be used (plus a 12mths booster dose if ongoing risk).

Diphtheria toxoid vaccine

This is a formaldehyde-inactivated preparation of diphtheria toxin, adsorbed onto alum to ↑ immunogenicity; given IM.

- Normally combined with DTP, but can be given as DT if pertussis is contraindicated.
- The vaccine does not prevent infection, but inhibits diphtheria toxin's effects, preventing systemic illness.
- A low-dose vaccine (combined with tetanus: Td) should be used in individuals >7yrs to ↓ risk of vaccine reactions.

Tetanus toxoid vaccine

A formaldehyde-inactivated preparation of TetT adsorbed onto alum given IM or deep SC. Normally administered to infants as part of DTP (but can be administered as DT if pertussis-containing vaccine is contraindicated).

- Recommended three doses in infancy, a booster at 12–23mths (DTPCV), and booster doses at 4–7yrs (Td) and 9–15yrs (Td) of age.
- In addition, administration of TetT to a pregnant woman (recommended two doses in first pregnancy) → IgG antibodies that cross the placenta and prevent neonatal tetanus.
- Supplementary mass immunization campaigns are recommended in countries of high risk for neonatal tetanus. Aim to immunize all women of child-bearing age.

Pertussis vaccines

Available in two forms: whole-cell vaccine (containing killed *Bordetella pertussis* bacteria, commonly used in most LMICs) or acellular vaccine (containing subunit pertussis toxin in combination with 1–4 other immunogenic pertussis proteins (i.e. filamentous haemagglutinin, pertactin and fimbriae)).

- Both vaccines given IM, normally as part of DTwP or DTaP.

- 1° immunization in early infancy is essential as pertussis mortality highest during early infancy (➲ Immunization strategies and schedules, p. 843).
- A 1° three-dose series of DTwP-containing vaccine is recommended, with the first dose ≥6wks age. A booster dose of DTwP is recommended.
- WHO recommends that countries currently using wP-containing vaccines do not change to aP-containing vaccines.
- Duration of protection following wP booster is ~6–12yrs and ~4–5yrs following aP formulations.
- DTaP does not confer mucosal protection or prevent transmission which DTwP is effective in doing.
- Adolescents and adults can be infected and transmit pertussis to susceptible infants.
- There is ↑ focus on vaccination of pregnant women with dTaP vaccines, to ↑ transplacental antibody to their infants and protect against disease during the first 2–3mths of age when the risk for severe pertussis disease and death is greatest.

Side effects

10–50% of infants experience mild reactions, e.g. local swelling, fever, and irritability after wP vaccine. Prolonged crying occurs in <1%; seizures and hypotonic episodes occur <1 in 1000–2000 vaccinations. These reactions are less common after aP. Following a severe reaction to DTwP, wP should be omitted from subsequent immunizations, either by using DT or aP vaccines. No association has been found between wP and chronic encephalopathy.

Haemophilus influenzae type b (Hib) conjugate vaccine (HibCV)

Hib polysaccharide-protein conjugated vaccine stimulates a T-cell-dependent immune response, → induction of memory responses.

- Given IM either alone or with DTP +/− HepB +/− IPV combination.
- Almost all countries include the HibCV in their immunization programmes.
- Vaccination has been highly effective in ↓ Hib meningitis and also ↓ radiologically confirmed pneumonia by ~25%.
- Booster doses are used in most resource-rich countries.

Pneumococcal polysaccharide-protein conjugate vaccines (PCVs)

Two conjugate vaccines are currently recommended: a 10-valent (PCV10) and 13-valent (PCV13) vaccine. The PCV10 includes protein D as the conjugating protein, which may provide some protection against non-encapsulated *Haemophilus influenzae* mucosal infection (a common cause of otitis media and possibly pneumonia). Similar to HibCV, PCV also induces a T-cell-dependent immune response → memory responses.

- 10- and 13-valent PCV vaccines provide similar coverage against the dominant serotypes causing invasive pneumococcal disease in LMIC.
- PCV is immunogenic in early infancy and → immunological memory.
- PCV protects against vaccine-serotype invasive pneumococcal disease (>85%), acute otitis media (>50%), and radiologically confirmed pneumonia hospitalization (~30% reduction).

- PCV also ↓ colonization by vaccine serotypes in the nasopharynx → interruption of transmission → protection of unvaccinated individuals, incl. adults at high risk for pneumococcal disease, once infant vaccine coverage rates are ~50%.
- EPI schedule recommends three doses, either as a three-dose 1° series (3p+0) or as a two-dose 1° series (spaced ≥8wks apart) and a booster dose at 9–15mths of age (2p+1 schedule).
- A two-dose 1° series at 6 and 14wks induces similar immunogenicity compared to a three-dose 1° series at 6, 10, and 14wks; with the advantage of using the third dose as a booster dose to sustain durability of protection; might be more effective in preventing nasopharyngeal colonization.
- By 2018, PCV had been introduced in the national immunization programme in 138 countries.

Pneumococcal polysaccharide vaccine (PPV)

- PPV contains 23 serotypes of pneumococcus.
- PPV is not sufficiently immunogenic in children <2yrs; immunity in older individuals may be limited or short lived, as it does not → immunological memory.
- PPV-23 could be used 1–2mths after priming with PCV in specific groups at ↑ risk for severe infection, e.g. sickle cell disease, chronic renal failure, immunosuppression, CSF leaks, asplenia, diabetes or chronic liver, heart or lung disease. This could ↑ coverage for those serotypes not included in PCV.
- In LMICs, routine immunization of the elderly and high-risk populations with PPV23 is not a priority.

Contraindications Acute infection.

Side effects

Hypersensitivity reactions may occur. These are more common following PPV23 reimmunization <3yrs.

Rotavirus vaccines

Two live oral vaccines are available against rotavirus, which causes ~50% of diarrhoea-related hospital admissions and ~40% of diarrhoea deaths in LMICs.

- A live attenuated vaccine (RIX 4414, Rotarix®) is given as a two-dose course.
- A pentavalent bovine-human reassortant vaccine (Rotateq®) is given as three doses.
- Both vaccines confer protection incl. against rotavirus types that are not included in the vaccine.
- Large-scale studies of both vaccines have shown them to be safe and highly effective against severe rotavirus disease. There is a small ↑ risk of intussusception (~1–2/100 000 infants) mainly after the first dose of vaccine, but this risk is far outweighed by the benefits of immunization.
- The first dose should be administered at 6–15wks, subsequent doses given ≥4wks apart. The manufacturer recommends the final dose should be <8mths, but WHO recommends that the rotavirus vaccines be given with DTP vaccines up until 2yrs.

Measles vaccine

A live attenuated virus given IM or SC. May be given as a monovalent vaccine or in combination with rubella, +/– mumps, +/– varicella (MR, MMR, MMRV).

- Normally given at 9mths, but can be given at 6 and 9mths to those at high risk and to susceptible children with recent exposure to measles.
- All children should receive two doses of measles vaccine. In countries with ongoing transmission and risk of mortality, the first dose during infancy and second dose between 12 and 24mths of age.
- In areas with high maternal HIV+ve, initial vaccination should be at 6mths to mitigate against the lower transplacental acquisition of measles antibody in children born to HIV+ve women, as well as more severe disease in HIV+ve children.
- For high-risk patients in an outbreak, PEP (measles vaccine within 3d of exposure or, if vaccine contraindicated, measles immunoglobulin within 6d of exposure) will modify/prevent symptoms.

Side effects Mild measles-like illness may occur in 5–15% of children 7–12d after immunization. Febrile convulsions occur in ~1 in 3000 children.

Rubella vaccines

A live attenuated vaccine, often given as part of combination vaccine with MR, MMR, and varicella (MMRV) and administered IM or deep SC.

- The main purpose of rubella immunization is to ↓ 1° infection in pregnant women and thus protect against congenital rubella syndrome in their offspring.
- Countries providing two doses of measles vaccine should consider using combination rubella/measles vaccines with the second dose of measles vaccine.
- This approach (ideally accompanied by an initial immunization campaign) is preferred to immunizing adolescent girls and females of childbearing age, as this → low vaccine coverage and ongoing circulation of rubella virus.

Contraindications Although no evidence that rubella vaccine is teratogenic, avoid immunizing women in early pregnancy. Women should be advised to avoid pregnancy for 1mth following immunization.

Human papillomavirus vaccines

- HPV-induced cervical cancer causes ~260,000 deaths worldwide, and immunization against HPV has been introduced in many high-income countries and some LMICs. Bivalent (HPV types 16 and 18), quadrivalent (HPV types 6, 11, 16, and 18) and 9-valent (HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) vaccines are licensed. All vaccines are effective against cervical cancer, and the quadrivalent and 9-valent HPV vaccines also protect against genital wart causing strains.
- Given IM and indicated esp. for females (and males if resources permit) at >9yrs, to prevent premalignant lesions and cancers affecting the cervix, vulva, vagina, anus, and anogenital warts caused by specific HPV types.
- The focus in LMICs has been females aged 9–14yrs, before onset of sexually activity with a two-dose schedule, to prevent cervical cancer.
- Vaccination of females ≥15yrs or males is recommended if feasible, cost-effective, and affordable.

Contraindications Pregnancy (limited safety data).

Side effects Pain at injection site, pyrexia (>10%). No association with onset of chronic conditions, including autoimmune disease, has been found.

Japanese encephalitis vaccines

Japanese encephalitis (JE) vaccines fall into four classes:

- *Inactivated mouse brain-derived vaccines*: less favourable safety profile; should be replaced by the newer generation JE vaccines.
- *Inactivated Vero cell-derived vaccines*: attenuated SA 14-14-2 strain vaccines (IXIARO® and JESPECT®) were licensed in 2009. In 2012, they were licensed in India (JEEV®) and since then in other Asian countries. Administration recommendations vary by product, generally as two doses 28d apart starting the 1° series at ≥6mths of age in endemic areas.
- *Live attenuated vaccines*: widely used in China, India, Cambodia, Sri Lanka, Nepal, and South Korea (SA 14-14-2) and administered SC at ≥8mths.
- *Live recombinant (chimeric) vaccines*: licensed in Australia in 2010 and used in a growing number of Asian countries (IMOJEV®, JE-CV®, ChimeriVax-JE®). The vaccine uses live attenuated YF virus as a vector for protective antigens from SA 14-14-2 and is administered as a single SC injection from ≥9mths.

Yellow fever vaccine

A freeze-dried preparation of live attenuated virus strain (17D strain) grown in egg embryos and given by SC injection.

- YF is endemic in 29 countries in sub-Saharan Africa (where by far the greatest burden of disease lies) and 13 countries in Central and S America. In these countries, infant YF immunization is recommended at the same time as measles immunization.
- Protection from a single dose of vaccine is life-long. Therefore, the validity of the YF vaccination certificate is now extended to the life of the person vaccinated.
- In order to ↓ risk of YF reintroduction, proof of immunization is required for travellers from YF-endemic countries to countries at risk for endemic YF.

Contraindications Anaphylactic reaction to egg, immunocompromised, and age <9mths, but can be given at 6–8mths if high risk of YF.

Side effects Minor reactions (e.g. headache, myalgia), in 10–30% of recipients. Uncommon reactions incl. vaccine-associated neurological disease, e.g. meningoencephalitis or peripheral neuropathy. This occurs in ~0.8/100,000 doses (1.8/100,000 in those >60yrs). Vaccine-associated YF-like illness, of variable severity, occurs in ~0.4 per 100,000 doses, but is commoner in those >60yrs.

Further reading

WHO/SAGE position papers for all EPI vaccines. Available at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Other vaccines not routinely included in public immunization programmes in LMICs

Meningococcal vaccines

Two forms of meningococcal vaccines exist: conjugate vaccines are preferred over polysaccharide vaccines due to potential for herd protection and ↑ immunogenicity, particularly in children <2yrs.

- The plain polysaccharide vaccines are available either as bivalent (A and C), trivalent (A, C, W-135), and quadrivalent (A, C, W-135, Y). These vaccines are used in outbreak control, however, protection ↓ after several years and, apart from serogroup A, are poorly immunogenic in infants. Polysaccharide vaccines are administered as a single dose to persons ≥2yrs old.
- Polysaccharide-protein conjugate meningococcal vaccines (in which meningococcal polysaccharide capsules are conjugated to carrier proteins) are currently available as monovalent (A or C) or quadrivalent (A, C, W-135, Y) or a combination vaccine with Hib (HibMenC).
- Monovalent serogroup C glyco-conjugate vaccines are routinely used in many resource-rich countries and a quadrivalent meningococcal serogroup A, C, W-135, and Y vaccine is recommended for adolescents in the USA.
- A monovalent serogroup A meningococcal conjugate vaccine (MenAfriVac), recommended as a one-dose schedule at 9–18mths, has been introduced across the 'meningitis belt' in Burkino Faso, Mali, Niger, Cameroon, Chad, Nigeria, Benin, Ghana, Senegal, and Sudan; it is highly >90% effective. There have, however, been further outbreaks of meningitis in these countries due to non-A meningococcal serotypes as well as from pneumococcal serotype-1.
- The poor immunogenicity of the meningococcal serogroup B polysaccharide capsule renders this unsuitable for use in a glycoconjugate vaccine. A vaccine (Bexsero®) based on subcapsular proteins is licensed in Europe and Australia.

Mumps vaccine

Consists of a live attenuated strain of the virus grown in chick embryo cells. It is normally given by IM injection with measles and rubella vaccines in the MMR triple vaccine at 12–15mths with a second dose at 2–6yrs.

Influenza vaccines

These may either be inactivated vaccines for IM injection or live attenuated vaccines for intranasal administration. Most vaccines contain three influenza strains (two influenza A and one influenza B), with quadrivalent vaccines (two A and two B strains) licensed in some countries. The haemagglutinin (H) and neuraminidase (N) antigens used in the vaccines are determined by WHO each year according to the anticipated prevalent strains. The 2009 emergence of novel influenza A H1N1 (swine 'flu) highlighted the challenges in planning for vaccine production in response to an influenza pandemic.

- WHO recommends that for countries which have influenza vaccine as part of their public immunization programmes, pregnant women be prioritized for vaccination at any stage of pregnancy.
- This protects the mother (~50% efficacy) and her young infant (~50%) against influenza.
- More recent data also indicate a 25% reduction in all-cause severe pneumonia in infants <6mths, born to women who received the inactivated influenza vaccine during pregnancy.
- Influenza vaccine needs to be ideally given prior to the influenza season (in countries with influenza epidemics). Year-round immunization should be suitable in countries (some tropical) where influenza virus circulation is perennial.
- Annual vaccination is required due to drifts in the circulating strains of influenza virus. Vaccine effectiveness is dependent on the closeness of genetic match between the vaccine and circulating strains, and vary from 0% to 70% year on year.
- In children, inactivated vaccine is indicated from 6mths onward, with two doses of vaccine spaced 1mth apart for children between 6mths and 5yrs, if not previously vaccinated. The effectiveness of inactivated non-adjuvant influenza vaccine in children is ~20–40% when there is a match with the circulating viral strains.
- Live attenuated influenza vaccine is only recommended for children >2yrs, and generally only available in high-income countries.

Cholera vaccine

Two types of oral cholera vaccines are available. Cholera vaccines should be used where cholera is endemic and considered in areas at risk for outbreaks, and have an effectiveness of ~80% which falls to ~50% after 2yrs. Travel immunization is only recommended for relief workers, or travellers to remote areas in which epidemics are occurring.

rCTB-WC vaccine

Based on killed whole cells of *Vibrio cholerae* 01 combined with a recombinant B subunit of cholera toxin. Given with bicarbonate buffer as two doses 1–6wks apart in adults and three doses 1–6wks apart in children 2–6yrs. The vaccine is not licensed for children <2yrs. If there is an ongoing risk of infection WHO recommend a booster dose every 2yrs (for those >6yrs) and every 6mths (for children aged 2–6yrs). rCTB-WC does not protect against *V. cholerae* 0139, a serogroup found in South Asia.

Bivalent oral vaccines

These are based on killed whole cells of *V. cholerae* strains 01 and 0139. Administered as two doses 2wks apart, and can be given without buffer to children aged >1yr. A booster dose is recommended after 2yrs.

Side effects Both types of oral vaccine are well tolerated. During a cholera outbreak, a single dose of cholera vaccine provides substantial protection.

Dengue vaccine

CYD-TDV is a tetravalent, live attenuated viral vaccine.

- Administered as three doses on a 0–6–12mth schedule.
- Indication: prevent dengue illness from dengue virus serotypes 1, 2, 3, and 4 in individuals 9–45yrs or 9–60yrs living in dengue endemic areas.

- Not recommended when seroprevalence is <50% in targeted age group.
- Not recommended for children <9yrs (safety concern in children 2–5yrs), pregnant and lactating women, HIV-infected, and/or immunocompromised individuals (limited safety data).
- The dengue vaccine has been shown to result in ↑ severe disease and ↑ hospitalizations from dengue in individuals seronegative at time of first vaccination, compared to unvaccinated individuals.
- WHO now recommends a 'pre-vaccination screening strategy', in which only dengue-seropositive persons are vaccinated, for countries considering vaccination as part of their dengue control programme.

Side effects Headache (>50%), malaise (>40%), and myalgia (>40%).

Hepatitis A virus (HAV) vaccines

There are six variations; four inactivated HAV vaccines used in most countries and two live attenuated HAV vaccines used only in China.

- Antibodies persist for >2yrs after a single dose of inactivated HAV vaccine, and for many years after a second dose.
- Given as two doses 6–12 up to 36mths apart (inactivated) or a single dose (live attenuated).
- Not licensed for infants <1yr.
- HAV vaccine is also available combined with HBV vaccine, administered as 3 doses at 0, 1 and 6mths.
- Vaccination with HAV vaccine is encouraged in areas of intermediate endemicity.
- The high force of infection by HAV in resource-poor countries → asymptomatic childhood infections, which are mainly mild and give life-long immunity. HAV vaccines are therefore not necessary in these settings, but are required as countries evolve socially and economically.
- Travellers from resource-rich countries to these resource-poor settings should be immunized.
- Clinical trials in outbreak settings have demonstrated effectiveness for post-exposure immunization with HAV vaccines.

Side effects Well tolerated; no serious adverse effects reported.

Varicella vaccine

Multiple formulations of a live-attenuated varicella vaccine are licensed; all are based on the OKA strain VZV and may either be in a monovalent preparation or in combination with MMR vaccine (MMRV). The latter vaccine is associated with ↑ risk of febrile convulsions.

- Countries introducing routine childhood varicella immunization should administer the first dose at 12–18mths.
- Routine VZV immunization in many HICs usually involves two doses of vaccine 1–2mths apart to ↓ the risk of 'breakthrough' infections.
- Recent studies suggest VZV vaccine is safe and immunogenic in immunocompromised individuals, including those with asymptomatic HIV; however, there are case reports of disseminated OKA strain infections following immunization in these populations.
- VZV vaccine prevents ~40% of cases of zoster (shingles) for which indication a single dose can be given to the over-50s.

Typhoid vaccine

Three typhoid vaccines types are currently licensed for use:

- Typhoid conjugate vaccine (TCV).
- Unconjugated Vi polysaccharide (ViPS) vaccine.
- Oral live attenuated Ty21a vaccines.

Typhoid conjugate vaccine

- Two new-generation TCVs are currently licensed: Typbar-TCV® and PedaTyph™; also known as Vi-TT conjugate vaccines.
- Both consist of the Vi polysaccharide conjugated to a TetT carrier protein.
- A single dose of Typhbar-TCV® (IM) is recommended in children ≥6mths and adults up to 45yrs in typhoid-endemic regions.
- TCV is preferred at all ages due to ↑ immunogenicity, use in younger children and ↑ duration of protection compared with the ViPS vaccine.
- TCV should be prioritized in countries with high burden of typhoid disease or antimicrobial resistance.
- PedaTyph™ is licensed and marketed in India only; however, data on immunogenicity and side effects are limited.

Unconjugated Vi polysaccharide vaccine

This is administered as a single dose by IM or SC injection, and is immunogenic in adults and children ≥2yrs. Duration of protection is uncertain; however, booster doses are recommended every 3yrs.

Oral live attenuated (Ty21) oral vaccine

The vaccine is recommended in adults and children >6yrs and is administered as three oral doses given 2d apart (travellers from the USA are advised to have a fourth dose). Re-immunization is recommended every 3–7yrs for those living in endemic regions. Antibiotics and antimalarials (proguanil, mefloquine) should be avoided during the 3d before and after vaccination as they may inactivate the vaccine.

Further reading

WHO/SAGE position papers for all other vaccines. Available at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers.

Administration of vaccines

- Use appropriate needle length (i.e. 25mm) when injecting IM vaccines in order to ↓ local reactions and, potentially ↑ immunogenicity.
- Administer IM vaccines to infants in the lateral aspect of the thighs, while children >12mths should receive vaccines in the deltoid muscle (Figs. 21.1 and 21.2).
- Separate injection sites by at least 2.5cm.
- If two live vaccines (➲ Transport and storage of vaccines, p. 844) are to be administered (with the exception of OPV), they should be administered either at the same time or at >1mth apart.
- Due to ↑ risk of lymphadenopathy, no vaccine should be administered into an arm used for BCG administration for 3mths after BCG.
- If an immunization schedule is interrupted, the schedule should proceed as if no interruption had occurred, i.e. there is no need to 'restart' an immunization schedule.

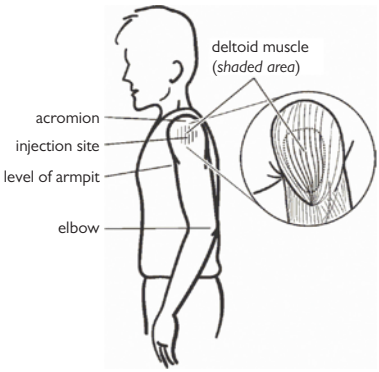

Fig. 21.1 Site of injection for children >1yr and adults. Reproduced with permission from Ramsay M, *Immunisation against infectious disease*, p. 28, Fig 4.1 (https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book) © Crown copyright 2017.

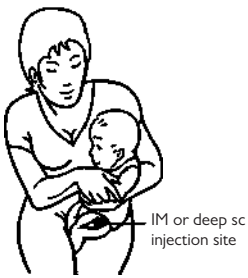

Fig. 21.2 Site of injection for infants <12mths. Reproduced with permission from Ramsay M, *Immunisation against infectious disease*, p. 28, Fig 4.2 (http://immunisation.dh.gov.uk/category/the-green-book) © Crown copyright 2017.

Health emergencies in humanitarian crises

Koert Ritmeijer

Introduction

Annually, >2.5 million people are uprooted due to armed conflict, repression, and natural or manmade disasters. Refugee and population displacements commonly occur in countries which lack resources or capacity to deal with them → an enormous economic, social, and ecological burden. Effective aid to refugee and displaced populations requires a rapid response, frequently with international support.

Mortality rates

- Mass population movements into areas with limited resources → high mortality rates (esp. in camp settings) that can be, during the first weeks/months following displacement, ~60× expected mortality rates. Relief programmes must begin promptly to ↓ excess mortality.
- Crude mortality rate (CMR) is calculated as deaths per 10,000 per day.
- In stable populations, CMR is <0.5 deaths per 10,000/d.
- In an emergency phase, CMR is >1 death per 10,000/d.
- The post-emergency phase (consolidation phase) starts when CMR falls to <1 per 10,000/d and basic needs have been addressed.

Priorities of intervention

In the emergency phase there are ten priority activities:

- Initial assessment.
- Measles immunization.
- Water and sanitation.
- Food and nutrition.
- Shelter and site planning.
- Healthcare.
- Control of communicable diseases and epidemics.
- Public health surveillance.
- Human resources and training.
- Coordination.

Ideally, these interventions should be carried out simultaneously. This becomes feasible when different teams of relief workers are involved.

Initial assessment

An initial assessment within the first few days is undertaken to:
- Identify health priorities.
- Plan the implementation of these priorities.
- Decide strategies.
- Determine resources needed.
- Work out a time frame.

The assessment includes six categories:
- *Geo-political context*:
  - Cause and duration of displacement, conditions under which it took place.
  - Security situation on the settlement site.
  - Human rights abuses.
  - Acceptance of refugees by host authorities and local population.
- *Description of the refugee population*:
  - Demography—estimate total population and age/sex distribution.
  - Socio-cultural characteristics—ethnic background, type of leadership and community organization, religion, particular customs.
  - Vulnerable groups—unaccompanied children, female-headed households, elderly, disabled, minority groups.
- *Characteristics of environment in which refugees have settled*:
  - Water supply—availability, quantity, and quality.
  - Physical characteristics (map), climate, accessibility, roads.
  - Types of shelter, % of refugees with proper shelters.
  - Density—surface area available per refugee.
  - General hygiene and disposal of excreta—defecation areas, type and number of latrines.
  - Presence of vectors transmitting communicable diseases.
- *Major health problems*:
  - Mortality rates and causes.
  - Morbidity data on the most common diseases.
  - Diseases with epidemic potential (cholera, shigellosis, measles, meningitis, hepatitis).
  - Acute malnutrition prevalence.
  - Vaccine coverage data (esp. measles, meningitis).
- *Requirements of human and material resource*:
  - Qualified staff among the refugee and host population.
  - Food available—existing food reserves, food rations distributed.
  - Cooking utensils, water containers, soap, blankets, clothes.
  - Existing health facilities.
- *Operating partners*.

Data collection methods are quantitative as well as qualitative, and is gathered by systematic observation, interviews with key persons, focus group discussions, sample surveys, and mapping. Methods are often ‘quick and dirty’, and results may need to be confirmed later with more in-depth methods.

Measles immunization

Measles kills one in ten children affected in resource-poor countries. In refugee emergencies, low vaccination coverage, overcrowding, and poor hygiene in camps are risk factors for the emergence of measles outbreaks, and malnutrition ↑ severity of measles and ↑ mortality (➲ Measles, p. 738).

Mass measles immunization should always be an absolute priority during the 1st week. Immunization of children from 6mths is recommended, as infection at an early age is common in high-density populations → high mortality. Because of low vaccine efficacy in young age, children 6–9mths must receive second dose as soon as possible after 9mths. Older children may also be susceptible, so target children aged 6mths–15yrs for mass immunization. All ages can be included if older age groups are also affected. Measles immunization is only contraindicated in pregnant women, because the vaccine contains live attenuated virus.

Mass vaccination can be accompanied by distribution of vitamin A (age 6–12mths 100,000IU; >1yr 200,000IU), and/or mid-upper arm circumference (MUAC) malnutrition screening of children <5yrs.

Measles vaccination coverage >90% is needed to prevent outbreaks; a vaccination campaign should be followed by a vaccination coverage survey (two-stage cluster sample (30 clusters of seven children)). If coverage <90% consider a catch-up campaign. Home visitors can check vaccination status and refer to immunization points. In refugee camps, immunize new arrivals (e.g. at reception/screening points) to sustain high coverage.

In the post-emergency phase, measles vaccination will be integrated within the Expanded Programme on Immunization (EPI).

Water and sanitation

Water supply

Drinking water is an absolute priority. Inadequate water supply and sanitation ↑ transmission of diarrhoeal and other diseases. During the 1st days of the emergency phase a minimum of 5L of water/person/d is required for drinking and cooking. During the next stage of the emergency phase, this must be rapidly ↑ to 15–20L/person/d to allow for personal hygiene and ↓ risk of epidemics.

- Existing water sources must be assessed, and open water sources (e.g. lakes, ponds, wells) protected to prevent contamination.
- Temporary water supply by tanker deliveries may be necessary until a more permanent supply (e.g. boreholes) is set up.
- Plastic bladders/tanks are often used for water storage, treatment, and distribution.
- Water quality should be checked with simple kits, and can be improved by chlorination (disinfection) and/or pre-treatment (sedimentation).

Excreta control

Water supply and latrines should be monitored in the same manner as disease incidence and mortality rates.

During the 1st days of the emergency phase, organize defecation areas or fields, shallow trench latrines, or collective latrines: one latrine or trench per 50–100 persons. Improve as soon as possible to one latrine per 20 persons, or ideally one per family.

Waste water control

Drainage trenches for rain-water avoid soil erosion and flooding during heavy rains. Waste water from washing areas and health facilities should drain into the soil.

Solid waste control Organize waste collection by cleaning teams and create land-fill. Incinerate contaminated medical waste from health facilities, before disposal in a pit.

Disposal of the dead

A cemetery or burial place should be planned.

Personal hygiene

Consider large-scale distribution of soap.

Vector control

Modify environment against vectors (insects and rats), e.g. control of insect breeding sites.

Preventive measures incl.: construction of latrines, draining of stagnant water, collection of waste, and personal hygiene.

Food and nutrition

Population displacement is generally either the cause or consequence of food shortages. Malnutrition is frequent in refugees and an important cause of mortality. Outbreaks of vitamin deficiencies (e.g. scurvy or pellagra) may occur.

Assessment of food and nutritional situation

- Food availability and accessibility:
  - *Information relating to food distributions*—theoretical food ration, ration actually distributed, distributing agency, target group, frequency of distributions.
  - *Assessment of local market*—type and price of food available.
  - Estimate the food basket of individual households by a sample survey.
- Nutritional status of the refugee population—prevalence of moderate acute malnutrition (MAM) and severe acute malnutrition (SAM) are assessed in children 6mths–5yrs by measuring MUAC or weight for height (W/H) (➲ Nutrition, p. 629). Global acute malnutrition (GAM) is the sum of SAM and MAM.
- *Other information which influences nutrition*: mortality rates, disease outbreaks, micronutrient deficiencies, water supply, climate and shelter, dietary habits, security, provision of health services.

Interventions

- Ensure an average > 2100kcal/person/d containing: 10% protein energy and 10% fat energy, and micronutrients.
- ↓ prevalence and mortality from malnutrition; treat SAM.
- Prevent malnutrition in groups at risk.

How to decide on nutrition interventions

Tables 22.1 and 22.2 can be used to help interpret the seriousness of a situation and select the appropriate type of intervention.

- *General food ration available*: if the ration is inadequate, improve the food supply. Consider selective feeding programmes. General food distribution is a major undertaking, usually carried out by specialized agencies. Registration and a census of refugees upon arrival are essential for estimating food needs and identifying beneficiaries. Monitor the basic food ration by regular random food basket surveys of households.
- *Malnutrition prevalence*: prevalence of acute malnutrition determines the level of intervention required. GAM >10% = a *food crisis*.
- *Aggravating factors*: if present, a higher level of intervention is required:
  - CMR >1/10,000/d.
  - Inadequate food ration (<2100kcal/person/d).
  - Epidemics of measles, *Shigella*, or other communicable diseases.
  - Severe cold and inadequate shelter.
  - Unstable situation, e.g. caused by a new influx of refugees.

There are three categories of interventions:

- Prevention programmes: general food distribution (GFD) for an entire population at risk, and targeted food distribution (TFD) or blanket supplementary feeding programme (BSFP) for vulnerable households or individuals.
- Nutrition treatment programmes: therapeutic feeding programme (TFP) and targeted supplementary feeding programme (TSFP) for treatment of acute malnutrition (➲ Nutrition, p. 629).
- Nutrition during illness.

Table 22.1 Food security classification

	Level	1	2	3	4	5
	Food security	Generally food secure	Borderline food insecure	Acute food crisis	Food/humanitarian emergency	Famine/humanitarian catastrophe
Food security indicators	Food access/ availability	Adequate and stable	Borderline adequate and/or seasonal variation	↓ resources; limited food access	Severe ↓ resources, unable to meet food needs	Extreme ↓ resources; starvation
	Kcal/person/day	>2100	~2100	<2100	<1600	
	Dietary diversity	Constant quality/ quantity, diversity	Chronic and/ or limited dietary diversity	Acute deficit and insufficient nutrient intake	Severe acute deficit and nutrient intake	Negligible
	Destitution/ displacement		Seasonal migration, mainly by men	Migration stretches in period and household members	Concentrated, often entire families	Large scale, concentrated
Nutrition	GAM WHZ*	<5 %	5–10%**	10–20%	20–40%	>40%
	GAM MUAC*		>7%	>15%	>20%	
	SAM WHZ**	<2%	<2–3%	3–7%	>7–10%	>10%
	SAM MUAC**	<1.5%	1.5–3%	3.5–5%	>5%	

	Level	1	2	3	4	5
Health	Morbidity	Under control	Under control, endemic diseases ↑	↑ morbidity, epidemics likely	Epidemic	Epidemic
	Crude mortality (deaths/10,000 people/d)	<0.5	<1	1–2	>2	>5
	<5yr mortality (deaths/10,000 children <5yrs/d)	<1	<2	>2	>4	>10
	Impact on healthcare system	Stable admission rates	Seasonal ↑ in admissions	Epidemic risk, nutrition programmes fail to cope	Healthcare system over whelmed	

* Global acute malnutrition (GAM): W/H <−2Z score WHO 2006 and/or bilateral oedema; or MUAC <12.5cm and/or bilateral oedema.

** Severe acute malnutrition (SAM): W/H <−3Z score WHO 2006 and/or bilateral oedema; or MUAC <11.5cm and/or bilateral oedema.

Table 22.2 Types of food and nutrition programmes

	Programmes	Objectives	Rations	Target groups	Food security level
Prevention	GFD General food distribution	Meet basic food needs	General food 2100kcal/person/d + Specific food for <2yrs	Entire population	4 and 5
	TFD Targeted food distribution	↑ food availability at household level	Food From 500 to 2100kcal/person/d + Specific food for <2yrs	Vulnerable households (e.g. headed by women or with a child <5yrs)	3 and 4 5: to wait for the GFD coming
	BSFP Blanket supplementary feeding programme	Improve diet quality for vulnerable individuals	Rations/needs From 125 to 500kcal/person/d	Vulnerable individuals (e.g. <3yrs; pregnant and lactating women)	2, 3, 4, and 5
	Infant feeding in emergency	Strengthen breastfeeding	No food given Referral to BSFP for pregnant and lactating women	Young infant <6mths and their mothers	4 and 5
Nutrition	TFP Therapeutic feeding programme	Treat SAM and its associated medical complications.	Ration/physiological needs Specific food	SAM patients	At all levels
	TSFP Targeted supplementary feeding programme	Treat MAM Prevent SAM	Ration/physiological needs Specific food	MAM patients	3, 4, and 5
	Nutrition during illness	Provide correct calorific, macronutrient, and micronutrient needs to encourage healing and recovery	Rations/needs Specific food	Sick patients and hospital patients	At all levels

Shelter and site planning

Poor shelter and overcrowding are major risk factors in the transmission of diseases with epidemic potential (e.g. measles, meningitis, typhus, cholera) and outbreaks of disease are ↑ in frequency and severity when population density is ↑. Provision of a secure living space, with protection against sun, rain, cold, and wind, and a sense of privacy is essential for refugee welfare.

Site planning

Security and protection: settlement must be safe (e.g. free of mines), and at distance from war zones.

- *Water*: must be available on the site or nearby (Table 22.3).
- *Space*: ensure 30m^2 per person.
- *Accessibility*: the site must be accessible during all seasons.
- *Environmental health risks*: no nearby vector breeding sites.
- *Local population*: avoid tensions arising between local community and refugees (e.g. land rights must be respected).
- *Drainage*: site should slope to provide natural drainage.

Table 22.3 Some quantified norms for site planning

Area per person	30m^2
Shelter space per person	3.5m^2
People per water point	250
People per latrine	20
Distance to water point	150m max.
Distance to latrine	30m
Distance between water point and latrine	100m
Firebreaks	70m every 300m
Distance between shelters	>2m

Basic healthcare

In emergency phase, basic healthcare focuses on acute respiratory infections, diarrhoea, malaria, measles, and malnutrition. Also address:

- *Physical trauma*: refugees may have been subject to violence → physical trauma → wound care or surgery.
- *Mental trauma*: a significant proportion will have suffered psychological trauma, → PTSD. Provide basic counselling services for individuals and groups. Absence of appropriate mental health services → ↑ burden in the outpatient department (OPD) with psycho-somatic complaints.
- *Sexual and reproductive health*:
  - Prevent and manage the consequences of sexual and sex-based violence—treat physical trauma and STIs, provide emergency contraception, PEP, hepatitis B vaccination, and mental health support.
  - Provide free condoms.
  - Ensure safe deliveries and organize referrals for obstetric complications.
  - Plan comprehensive reproductive health services, e.g. ante- and post-natal care, tetanus immunization, STI and HIV screening, prevention of mother-to-child transmission of HIV.
  - HIV and TB—provide ART or TB treatment.

Healthcare systems in refugee emergencies

- Provide treatment for common communicable diseases.
- ↓ suffering from other debilitating diseases.
- Carry out active case finding.
- Anticipate a high demand for care.
- Ensure access to different levels of care, including referrals.
- Deal with the majority of illnesses at a basic level of care.
- Assist surveillance activities, e.g. data collection.
- Combine curative and preventive services.
- Adapt flexibly to changes, e.g. outbreaks of disease.

Levels of healthcare A four-tier healthcare model is useful (Table 22.4):

Referral hospital

Specialized hospital services, e.g. for surgery or major obstetric emergencies. May be provided in an existing hospital near the settlement, often the hospital needs to be strengthened. Establish referral protocols to avoid refugee self-referral; organize transport. In the case of large camps, field hospitals should be established on site.

Central health facility (health centre)

Able to deal with most illnesses, offer 24h services, and possibly basic in-patient service. Establish a good triage system to deal with the large number of patients presenting.

Peripheral health facilities (health post or health clinic)

Decentralized, easily accessible to all. This first-line OPD deals with only a few killer diseases, e.g. diarrhoea and malaria, with a limited list of essential drugs, and refers serious cases to the health centre. It also provides treatment for a few, non-life-threatening diseases (e.g. scabies, conjunctivitis).

Community health workers

A community outreach programme links the fixed health facilities to the population. Duties: active case finding, surveillance, directly observed TB treatment, health promotion, and community mobilization, e.g. for vaccination campaigns. The network of community health workers based in the population requires training and supervision. Basic tools are essential: treatment protocols, list of essential drugs at each level, referral system, good coordination, system of data collection. National health authorities should be involved.

The WHO Emergency Health Kit includes medicines, disposables, and instruments, sufficient for 10,000 people during a 3mth period.

Table 22.4 Levels of healthcare and activities they can carry out

Level	Population coverage	Activities	Clinical staff per facility
Referral hospital	Variable	Surgery Major obstetrical emergencies Referral laboratory	Doctors: variable 1 nurse per 20–30 beds, 8h shifts
Central health facilities (health centre)	1/10,000–30,000 refugees	Triage OPD (1st level and referral) Dressing and injections ORT Emergency service (24h) Uncomplicated deliveries Minor surgery Pharmacy Basic laboratory tests Blood transfusions Immunizations	Min. 5 medical staff: 1 doctor 1 HW for 50 consultations/d 1 HW for 20–30 beds, 8h shifts 1 HW for ORT 1–2 HW for pharmacy 1–2 HW for dressings/injection/sterilization
Peripheral health facilities	1/3000–5000 refugees	OPD (first level) ORT Dressing Referral of patients to higher level	Min. 1 HW, based on 1 person for 50 consultations/d 1 non-medical for ORT, dressing, registering
Outreach activities (home-visitors)		Home visits and active screening Referral of patients to facilities Health education, information	1 CHW per 500–1000 referrals 1 supervisor for 10 CHWs 1 senior supervisor

CHW, community health worker (limited training; may not be clinically qualified); HW, health worker (includes nurses, health assistants, medical assistants, midwives); OPD, outpatient department; ORT, oral rehydration therapy.

Control of communicable diseases and epidemics

During the emergency phase, the highest morbidity and mortality are from:

- Measles.
- Diarrhoeal diseases.
- Acute respiratory infections.
- Malaria.
- Outbreaks of cholera, *Shigella*, meningococcal meningitis, diphtheria, typhoid, or hepatitis E → high mortality.

Objectives of epidemic control

To ↓ transmission and ↓ mortality among cases:

- ↓ *sources of infection* by prompt diagnosis and treatment (e.g. cholera), isolation (e.g. VHFs), or controlling animal reservoirs (e.g. plague).
- *Protect susceptible groups*: immunization, better nutrition, or chemoprophylaxis of high-risk groups (e.g. intermittent presumptive treatment for malaria among pregnant women and children <5yrs).
- *Interrupt transmission* by improvements in environmental and personal hygiene, health education, vector control, disinfection, and sterilization.

General measures for communicable disease control

- General preventive measures consist mainly of improving the environment and living conditions of refugees. ↓ overcrowding, provide shelters, ensure water supplies, excreta disposal, food supply, vector control. Mass immunization against measles always high priority.
- Outreach activities by home visitors for early case finding and active screening, covering the whole population. Suspected cases rapidly referred to health facilities.
- A basic health system to ensure early and adequate treatment of measles, diarrhoeal diseases, acute respiratory infections, and malaria.
- A good surveillance system, allowing early, appropriate outbreak response (Table 22.5).
- Prepare contingency plans in advance (e.g. for cholera).

Epidemic preparedness

Contingency plans should be prepared to enable health teams to react quickly if an epidemic is declared.

- Gain information on potentially epidemic diseases that already occur in the area or which might be introduced.
- Have a surveillance system ready to detect diseases as soon as they appear. Use standard case definitions, and train health staff in use of case definitions.
- Consult standard protocols for prevention, diagnosis, and treatment. Adapt protocols to the local conditions, the skill of HWs, characteristics of the causative agent (e.g. drug resistance and serotype), background immunity of the refugee population. Seek the help of experts.
- Identify a laboratory for confirmation of cases. Sample containers for stool and blood tests should be available, and RDTs. Identify a reference laboratory at regional or international level, e.g. for antibiotic sensitivity testing of *Shigella* or identification of VHFs.

- Identify sources of relevant vaccines for mass campaigns (e.g. measles or meningitis).
- Prepare, and store on site, emergency stocks (e.g. ORS, IV fluids, vaccines, tents, plastic sheeting, cholera kits).
- Identify possible treatment sites (e.g. cholera treatment centre).
- Assess the availability and skills of staff who would respond to outbreaks. Upgrade skills by training.

Table 22.5 Steps in outbreak investigation

Activity	Comments
1. Confirm outbreak and diagnosis	• Diagnosis verified (clinical and laboratory)? • Link between cases? Expected numbers? • Immediate control measures needed (e.g. prophylaxis, isolation, public warning, hygiene measures)? • Further investigation needed? Create outbreak investigation team
2. Case definition and identification	• Clinical criteria, restrictions in time, place, person • Simple, practical, objective, sensitive
3. Descriptive data collection and analysis	• Orient cases by time, place, and person • Analyse where, when, who
4. Develop hypothesis	• Risks, cause, source, vehicle, mode of transmission? • Compare hypothesis with facts
5. Analytical studies to test hypothesis	• Analytical epidemiological studies: cohort, case–control; prospective. retrospective
6. Complementary special studies	• Environmental surveys, microbiological surveys
7. Implementation of control measures	• Don't wait until the end of the investigation • *Source*: remove source of contamination (e.g. chlorination of water) • *Transmission*: remove persons from exposure (e.g. hygiene measures) • *Carrier*: isolate and/or treat infected persons • *Susceptibility*: inactivate/neutralize pathogen (e.g. vaccination)
8. Communication, incl. outbreak report	• Document the event and make synthesis • Communicate to authorities and public • Propose recommendations • Lessons learned

Public health surveillance

Surveillance measures and monitors the health status of a population, and regularly generates information.

Objectives

- To provide early warning of epidemics with outbreak identification and investigation.
- To monitor the main health problems and trends over time.
- To assist planning of interventions and targeting of resources.
- To evaluate the coverage and effectiveness of programmes.
- To provide information on the refugee situation (for witnessing).
- To constitute a data bank for training or operational research.

Principles

- During the emergency phase, data collection should only focus on health problems which produce the highest mortality and morbidity.
- Data collection should be limited to problems that can be effectively prevented or treated.
- The system should be as simple and flexible as possible.
- The frequency of data transmission and analysis should be adapted to the situation, i.e. weekly in the emergency phase and monthly thereafter.
- Responsibility for organizing and supervising the surveillance system should be clearly assigned, and close coordination between all partners (United Nations agencies, NGOs, and the host country's Ministry of Health) is essential.
- Data analysis should take place in the field, where it will be translated into action.

Data coverage and sources

- *Demography*: total and <5yrs population, new arrivals and departures; (source: United Nations agencies, community leaders, home visitors, rapid household sample surveys).
- *Mortality*: CMR and <5yrs mortality rates, cause-specific mortality rates; (source: grave counts, hospitals, home visitors, community leaders).
- *Morbidity*: disease incidence and attack rates (per 1000/wk) (source: OPD and inpatient health services, home visitors).
- *Basic needs*: water quantity, food availability, sanitation, shelter, other needs (source: agencies in charge of specific services).
- *Programme activities*: consultations/wk, attendance rate, admissions/wk, hospital mortality rate, measles vaccine coverage. (source: registers of the programmes concerned).

The daily CMR is the most useful health indicator to monitor the health status of a refugee population. The CMR is the number of deaths per 10,000 population per day. A CMR >1 indicates an emergency situation (Table 22.6). Because high <5yrs mortality (U5MR) may be masked by the CMR, mortality in this age group is monitored separately. Calculating disease-specific mortality rates helps in determining the major killer diseases and establishing priorities.

Table 22.6 Mortality classification

	CMR (deaths/10,000/d)	U5MR(deaths/10,000/d)
Stable population in resource-poor countries	<0.5	<1
Refugees/displaced		
Under control	<1	<2
Emergency	>1	>2
Out of control	>2	>4
Catastrophic	>4	>8

Human resources, coordination, and management

A refugee emergency response requires personnel, coordination, and management.

Human resources and training

Large numbers of personnel are required: public health doctors, sanitation specialists, nutritionists, logisticians, administrators. They will require formal and on-the-job training. Home visitors are particularly important to ensure the link between the refugee community and assistance programmes, and they should be recruited at the start, from among the refugee or displaced population. Although there may be qualified HWs among the refugee population, employment is usually not simple, depending on the legal status of refugees, and recognition of qualifications by the host country. It is usually necessary to organize training courses on:

- Conducting mass measles immunization.
- Data collection.
- Essential drugs and standard treatments.
- Conducting surveys.
- Environmental health measures.
- Specific measures to take during epidemics.
- Oral rehydration.
- Active screening for those who are sick and/or malnourished.
- Safe deliveries.

Coordination

- Coordination between agencies must be established in the early phase, and leadership defined. If the initiative has not been taken by United Nations High Commission on Refugees (UNHCR) or the host government, relief organizations should organize a coordination team and may need to take on the leadership role.
- The host government should participate in the coordination process; government ministries (e.g. health and water) should be involved.
- The UNHCR plays a major role in the coordination of refugee programmes. Its mandate includes responsibility for ensuring protection and the adequate care of refugees and may also be extended to cover internally displaced populations.
- Common objectives and distribution of tasks should be agreed upon and followed by all involved.
- Regular meetings and reporting must be formalized to ensure information exchange and decision-making.
- Technical guidelines, standard policies (including standard data collection) should be introduced from the beginning, and adapted to the situation after the emergency period.

Camp management

Covers different areas:

- Administrative organization of the camp and its population (incl. involvement of community representatives).
- Organization of the site and installation of infrastructure.
- Reception structure for new arrivals, incl. screening and registration.
- Organization of efficient and equitable system of general distributions.
- Organization of staff.

Post-emergency phase

The post-emergency phase begins when the CMR falls to <1 per 10,000/d and basic needs have been addressed. Disease patterns become roughly the same as those in any non-refugee population, though refugees are still at ↑ health risk than stable populations, and other diseases, such as reproductive health problems, HIV/AIDS, TB, and mental problems, may account for significant morbidity/mortality. Infectious disease epidemics continue to occur. Low levels of malnutrition commonly persist, as refugee populations continue to be dependent on food distributions, and inadequacies in the food rations often continue.

Objectives of interventions in the post-emergency phase

- *Consolidating what has already been achieved*: low mortality, good nutritional and health status.
- *Preparing for possible new emergencies*: major disease outbreaks or an influx of new refugees/displaced.
- *Achieving a certain level of sustainability*: ↓ assistance in line with ↓ needs, better use of local resources, training.

Specific issues will take on greater importance:

- Curative healthcare (integrating preventive and curative care, adaptation to host country health system, improvement of quality).
- Reproductive healthcare (antenatal care, safe delivery, postnatal care, family planning, sexual and gender-based violence, female genital mutilation).
- Child healthcare (IMCI, EPI, feeding programmes).
- HIV, AIDS, and STI programmes (prevention, testing, treatment).
- TB programmes (testing and treatment for drug-susceptible TB and MDR-TB).
- Psycho-social and mental health (management of PTSD, prevention of psycho-social problems, prevention, and management of psychopatholo gies).

Chapter 23

Obstetric emergencies

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Introduction

Annually, ~300,000 women die from pregnancy- or childbirth-related complications. Most maternal mortality is preventable and mainly occurs in resource-poor settings. Reducing maternal mortality and morbidity should be an international priority. Most maternal mortality occurs in a critical 24h window. Clinical guidelines and relevant publications from the WHO can be found at: http://www.who.int/reproductivehealth/topics/en/.

Guidelines should be tailored according to the local situation, e.g. https://publichealth.ku.dk/about-the-department/global/research/partoma-project/.

Remember: suspect pregnancy in any collapsed woman of childbearing age.

Respectful maternal care

All women, newborns and their families deserve respectful care. During emergencies, stress and anxiety can be ↓ by reassurance and explanation. Emotional and psychological support, including information and counselling after birth or adverse events, → optimal outcomes and may ↓ future psychological trauma.

Antenatal care

Antenatal care allows for estimation of gestational age, nutritional interventions (e.g. ferrous/folate), immunizations, assessment and management of anaemia, hypertension, gestational diabetes mellitus, infections, fetal growth, and identification of malpresentation peripartum depression, and partner violence. Effective antenatal care can ↓ potential obstetric emergencies.

Early pregnancy bleeding

Vaginal bleeding, +/– abdominal pain, in the first 22wks of pregnancy.

Management

- Assess ABC (➲ inside front cover of this handbook) and resuscitate with IV fluids.
- Clinical assessment to determine cause (Table 23.1).
- Urine human chorionic gonadotropin (HCG) test and pelvic USS where available. Take urine sample using catheter in collapsed patient; FBC and blood group/save.
- For inevitable or incomplete miscarriage give a single dose of 600 micrograms misoprostol orally (🖰 http://www.misoprostol.org/). Immediate evacuation (e.g. by manual vacuum aspiration) may be necessary if heavy bleeding.
- For septic miscarriage (fever, +/– purulent vaginal discharge), start broad-spectrum IV antibiotics for 24h before uterine evacuation.
- For suspicion of unsafe termination of pregnancy examine for signs of uterine, vaginal, or bowel injury. Carefully remove any materials from the vagina.
- For suspected or confirmed ectopic pregnancy, resuscitate and proceed immediately to surgery to control haemorrhage.
- Suspect molar pregnancy if there is passage of vesicles and a boggy uterus larger than dates.
- Consider Rh-immunoglobulin for Rh −ve women.
- Always advise on contraceptives—preferably long-acting reversible type—before discharge from hospital.

Table 23.1 Causes of vaginal bleeding and/or pain in early pregnancy

	Threatened miscarriage	Inevitable miscarriage	Incomplete miscarriage	Ectopic pregnancy
History				
PV bleeding	Light bleeding	Heavy bleeding No POCs passed	Heavy bleeding POCs passed	Light bleeding
Pain	Cramping, suprapubic	Cramping, suprapubic	Cramping, suprapubic	Severe Often unilateral
Examination				
Cervical os	Closed	Dilated	Dilated	Closed
Abdomen		Tender uterus	Tender uterus	Tender adnexal mass Haemo-peritoneum
Size of uterus	Equal to dates	Equal to dates	Small for dates	Small for dates
Investigations				
Pregnancy test	+	+	+	+/−
USS	Viable intrauterine pregnancy	POCs *in utero*	POCs *in utero*	Empty uterus Adnexal mass Free fluid on USS

POCs, products of conception; PV, per vaginam.

Hypertensive emergencies

Severe pre-eclampsia

BP ≥160mmHg systolic and/or ≥110mmHg diastolic *with* proteinuria ≥2+ on urine dipstick and/or severe maternal symptoms or danger signs (*neurologic*: headache, visual disturbance, hyperreflexia; *pulmonary*: difficulty breathing; *hepatic*: upper abdominal pain) diagnosed after 20wks' gestation.

Management

- Monitor BP, pulse, RR, tendon reflexes, urine output.
- Check for indications for immediate delivery.
- BP needs rapid correction. Aim for systolic <160mmHg and diastolic <110mmHg. Use nifedipine, labetalol, or hydralazine (Box 23.1).
- *Measure*: FBC, U&E, LFTs, and clotting where available.
- Definitive treatment is delivery.
  - Gestational age < limit of viability (usually 24–28wks, depending on setting): $MgSO_4$, antihypertensive medications, induce labour.
  - Gestational age between limit of viability and 34wks: $MgSO_4$, antihypertensive medications, corticosteroids, close maternal and fetal monitoring offering comprehensive obstetric care; expedite delivery if maternal or fetal status not stable.
  - Gestational age between 34 and 37wks: same management as previous, but no corticosteroids.
  - Gestational age >37wks: $MgSO_4$, antihypertensive medications, expedite birth.

Box 23.1 Indications for immediate delivery in pre-eclampsia

- *Neurologic*: frontal headache, visual disturbance, papilloedema, hyperreflexia, clonus, eclampsia.
- *Pulmonary*: crackles on chest auscultation due to pulmonary oedema.
- *Hepatic*: upper abdominal pain +/– vomiting, liver enzymes elevated >2× baseline.
- *Renal*: oliguria, serum Cr elevated >2× baseline.
- *Haematologic*: platelet count <100 × 10^9/L.
- Uncontrollable BP.

Eclampsia

Occurrence of generalized tonic–clonic seizures in association with pre-eclampsia and in the absence of any other cause. Exclude hypoglycaemia, meningitis, or malaria.

Eclampsia may be the first presentation of pre-eclampsia and should be considered in all pregnant women with seizures.

Management of eclampsia

- Get assistance and resuscitate if needed (assess ABC, see ➲ inside front cover of this handbook).
- When safe, place in left lateral position and obtain IV access.
- Send blood for FBC, U&E, LFTs, glucose, malaria test, and clotting where available.
- Perform bedside clotting test: failure of a clot to form <7min or formation of a soft clot that breaks down suggests coagulopathy.

Box 23.2 Treatment

Seizures

Magnesium sulfate is the first-line treatment for seizures. Inform the patient about $MgSO_4$ side effects, e.g. intense warmth feeling. Be aware of magnesium toxicity: delay next dose if RR <16/min, absent reflexes, or urine output <30mL/h over 4h.

Loading dose

- 4g $MgSO_4$ IV over 5–15min (usually in 20% solution).
- Follow with 5g of 50% $MgSO_4$ with 1mL of 2% lidocaine in same syringe IM into each buttock (10g total dose).
- If further seizures (after 15min), give an additional 2g $MgSO_4$ (50%) solution IV over 5min.

Maintenance dose

- 5g of 50% $MgSO_4$ with 1mL of 2% lidocaine in the same syringe every 4h into alternate buttocks, or 1g per hour IV infusion if this can be closely monitored.
- Treatment should continue until 24h after delivery or the last seizure, whichever is later.

Treat hypertension

If BP >160/110mmHg, give nifedipine (10mg orally, modified release, *avoid rapid-acting sublingual preparations*), oral labetalol 200mg or 20mg IV slowly, or hydralazine 5mg IV slowly, repeated after 20min if necessary.

Beware of fetal distress in cases of rapid ↓ in BP. Aim for systolic of 120–140mmHg and diastolic of 90–100mmHg.

Treat coagulopathy

Give blood/blood products as available.

For more information (and dosing for magnesium infusion rather than IM, if available): https://apps.who.int/iris/bitstream/handle/10665/255760/9789241565493-eng.pdf.

- Measure and monitor BP, pulse, RR, tendon reflexes.
- Check for pulmonary oedema.
- Insert urinary catheter and monitor input/output; fluid restrict to 80mL/h IV. Keep nil by mouth.
- Treat as per Box 23.2.

Eclampsia, any gestational age: if undelivered

Assess fetal well-being only once mother is stable. Aim for birth within 12 hours:

- Cervix favourable: artificial rupture of membranes and oxytocin.
- If fetal death confirmed, pre-viable live fetus, unfavourable cervix *or* unsafe anaesthesia → induction of labour with misoprostol or catheter.
- Maternal or fetal necessity and safe anaesthesia available → caesarean section.
- Continue maintenance $MgSO_4$ (as in Box 23.2).
- Observe women with severe pre-eclampsia for >72h post delivery as 44% of seizures occur in this time.

HELLP syndrome

A variant of severe pre-eclampsia characterized by HELLP (haemolysis, elevated liver enzymes, and low platelets) and with significant maternal and perinatal morbidity and mortality.

Diagnosis RUQ/epigastric pain (liver capsule swelling) alongside usual symptoms of pre-eclampsia with evidence of HELLP on FBC and LFTs.

Management Delivery. Manage as eclampsia.

Pregnancy-related infection

Pregnancy predisposes to infection and sepsis. Maternal sepsis is a life-threatening condition: organ dysfunction resulting from infection during pregnancy (Box 23.3), childbirth, post abortion, or postpartum period. Early recognition and aggressive management → ↓ maternal and neonatal morbidity and mortality.

Chorioamnionitis

Cause

Bacteria from the perineum and genital tract ascend into the uterus after rupture of fetal membranes.

Diagnosis

Maternal fever, tachycardia, uterine tenderness, offensive vaginal discharge, fetal tachycardia. Patients with prolonged rupture of membranes are at ↑ risk of chorioamnionitis.

Management

Delivery and broad-spectrum IV antibiotics; e.g. ampicillin 2g IV qds plus gentamicin 5mg/kg IV od plus metronidazole 500mg IV tds. There is no place for conservative management. Inhibiting labour should be avoided. Use steroids (for fetal lung maturation) with caution and do not delay delivery until after steroid administration.

Puerperal pyrexia

Maternal temperature ≥38°C within 14d of delivery.

Causes

Endometritis, retained POCs, perineal infection, breast abscess/mastitis, UTI, venous thromboembolism, wound infection.

Management

- Determine likely source and give appropriate antibiotics.
- Remove retained POCs.
- For genital tract sepsis, give antibiotics as for chorioamnionitis.
- For mastitis, cover *Staphylococcus aureus* (e.g. flucloxacillin). Consider surgical drainage if breast abscess.

Box 23.3 Preterm prelabour rupture of membranes

- Antibiotic prophylaxis is recommended: erythromycin 250mg qds oral for 10d or until birth (whichever is sooner).
- https://www.nice.org.uk/guidance/ng25/.
- Antenatal corticosteroids should be administered <34wks.
- Delivery should be considered from 34wks' gestation.

Obstetric haemorrhage

Haemorrhage is the leading cause of maternal mortality worldwide. Healthy women can have catastrophic, unpredictable blood loss. Continuous slow bleeding is an emergency as much as sudden haemorrhage.

Management of obstetric haemorrhage

- Call for help, stabilize mother (ABC see ➔ inside front cover of this handbook) and provide high-flow O_2 via face mask.
- Insert two large IV cannulae, take FBC, and cross-match blood. Resuscitate with IV fluid. Insert urinary catheter—monitor input and output hourly.
- Check for coagulopathy (whole blood clotting test).

If undelivered

- Consider delivery once stable.
- Give blood/blood products as required.
- Consider transfer to a facility able to perform CS depending on the cause of bleeding (Box 23.4).

If delivered

- Massage the uterine fundus and rub up a contraction.
- Remove any clots from the uterus.
- Give 5IU of oxytocin IM if not given and try to deliver the placenta (examine: placenta complete?).
- Catheterize the bladder or check catheter position if already inserted.
- Inspect for causes of bleeding as listed in Box 23.4.
- To stop the bleeding, consider bimanual compression or (external) aorta compression.
- If blood loss persists, use the following drugs in sequence:
  - Tranexamic acid 1g IV, repeat after 30min.
  - Ergometrine 200 micrograms IV every 15min up to five doses (max. 1mg) (give IM if IV route difficult). Avoid if possible in pre-eclampsia/eclampsia.
  - Give 10IU oxytocin IV bolus and continue oxytocin 20IU in 1L crystalloid IV at 60 drops/min.
  - Give 800 micrograms of misoprostol sublingually (🖱 http://www.misoprostol.org).
  - Give blood products as available.

Box 23.4 Assessing and managing emergencies related to bleeding

Antepartum haemorrhage

- Placenta praevia (painless bleeding, high presenting part, USS placental location). Resuscitate and immediate transfer to surgical facility.
- Placental abruption (painful bleeding, firm, and tender uterus). Resuscitate; expedite delivery or immediate referral to surgical facility.

Intrapartum

- Ruptured uterus (severe pain, maternal shock, loss of presenting part). Resuscitate and immediate transfer to surgical facility.
- Ectopic pregnancy (➲ Early pregnancy bleeding, p. 883).

Postpartum haemorrhage

Four Ts—exclude these for every case of postpartum haemorrhage:

- *Tone:* uterine atony. Expel clots, rub contraction, empty bladder, administer uterotonic drugs.
- *Tissue*: retained products. Empty bladder. Examine uterine cavity. Remove tissue, membranes, and clots.
- *Trauma:* perineal trauma/cervical tears. Compress and suture.
- *Thrombin:* DIC. Give fresh, whole blood to replace red cells and clotting factors.
- Surgical treatment (intrauterine balloon tamponade, uterine compression sutures, artery ligation or hysterectomy) may be needed: seek senior help early. Reassess blood loss. Keep systolic BP >100mmHg and urine output >30mL/h.

Intrapartum emergencies

Cord prolapse

Umbilical cord prolapsed below the presenting part after the rupture of membranes. Cord may be visible at the vagina or felt during vaginal examination. Determine cervical dilatation and whether cord is pulsating.

- *Cord pulsating, cervix not fully dilated*:
  - Deliver as soon as possible by emergency CS. Relieve cord compression by keeping patient in knee–chest position or pushing presenting part up.
  - For long transfers or delays before surgery, fill bladder with 500–750mL of saline using Foley catheter. Clamp catheter once filled, and document this carefully. Check fetal heart rate.
- *Cord pulsating, cervix fully dilated*: delivery by rapid assisted vaginal delivery.
- *Cord not pulsating*: confirm fetal demise. Deliver vaginally unless there is another indication for CS.

Shoulder dystocia

Impaction of the anterior shoulder against the maternal symphysis pubis after the fetal head has delivered (http://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg42).

Diagnosis

- Head remains tightly applied to the vulva—the 'turtle sign'.
- Chin retracts and depresses the perineum.
- Gentle traction on the head fails to deliver the shoulder.

Management—acronym HELPERR

- Call for **H**elp.
- **E**valuate for episiotomy and perform one if needed.
- **L**egs: flex thighs, abduct and rotate legs outwards (McRoberts).
- Apply suprapubic **P**ressure using the heel of the hand of an assistant from the side of the fetal back in a downward and lateral direction to rotate the anterior fetal shoulder into the wider oblique pelvic diameter.
- **E**nter—internal rotational manoeuvres—using a finger in the vagina attempt to manipulate the fetus to rotate the anterior shoulder into an oblique plane to deliver.
- **R**elease the posterior arm by grasping the radius, flexing the elbow, and sweeping it across the chest.
- **R**oll the patient over to all-fours position and deliver shoulder or remove posterior arm.

Breech delivery

- Fetus presents with buttocks or feet first. Identified on abdominal palpation and confirmed by USS or vaginal examination during labour. Significant ↑ in maternal morbidity and perinatal mortality.
- Has external cephalic version been offered? If not, consider external cephalic version if membranes intact.
- Consider elective CS according to the local policy (explain implications of CS for current and future pregnancy).
- Prerequisites for vaginal delivery: complete or frank breech, adequate pelvis, a fetus that is not large for dates and no previous CS, mother wants vaginal birth and understands risks (Box 23.5).

Box 23.5 Vaginal breech delivery

- Confirm full dilatation. Contractions should be regular and strong.
- *Hands off:* await spontaneous delivery of the buttocks. Maintain fetus in sacro-anterior position. Await delivery of inferior border of scapulae.
- Using the index finger, hook down arms at the elbows and bring them down to the chest.
- If the arms are stretched above the chest and cannot be reached, perform *Løvset's manoeuvre*. Place hands around hips with thumb on the sacrum. Rotate baby 180° clockwise to release the arm. Repeat in counterclockwise direction for other arm.
- *Mauriceau–Smellie–Veit manoeuvre:* When nape of neck is visible, place two fingers of one hand over maxilla and two fingers of the other hand at back of head to flex it. Assistant provides suprapubic pressure to aid head flexion.

Obstructed labour

Labour is obstructed when there is failure to progress despite strong, regular contractions. Often due to mechanical problems, e.g. cephalopelvic disproportion, malpresentation, or malposition.

Suspect obstruction when there is slow cervical dilatation and a presenting part that remains high despite good contractions and ruptured membranes. Labour progress depends on 5Ps: power, passage, passenger, pain/psyche, and 'pee (full bladder)'. Partograph → early diagnosis and intervention before complications develop.

Clinical features

- Prolonged labour (>12h) with maternal exhaustion and severe pain.
- *Maternal examination*: tachycardia and pyrexia are common.
- Strong uterine contractions with formation of a retraction ring (Bandl's ring). Fetal distress or fetal death may be present.
- *Vaginal examination*: ruptured membranes, an oedematous cervix, severe moulding, and a large caput.

Management

- Insert IV line and resuscitate. Catheterize the bladder (insertion may be difficult).
- Give broad-spectrum IV antibiotics and prepare for urgent delivery.
- Prepare for neonatal resuscitation.
- Exclude uterine rupture.
- *Preferred mode of delivery*:
  - First stage or unengaged head (2/5th or more palpable per abdomen) or not cephalic position → CS.
  - Second stage, engaged fetal head → assisted vaginal delivery.
- *Postoperatively:* bladder catheter should remain for up to 10d to prevent fistula formation. Give IV antibiotics as indicated. Counsel on future pregnancies: early antenatal booking and delivery in healthcare facility.

Healthcare-associated infection, antimicrobial prescribing, and antimicrobial resistance

Nicole Stoesser

Healthcare-associated infection

Healthcare-associated infections (HAIs) are a large, under-recognized, and largely preventable burden of disease affecting >15% of patients in resource-poor settings (Box 24.1). Hospitals bring patients and HCWs into close proximity with a wide range of potential transmission risks, incl. infected/colonized individuals and contaminated equipment/environments. HAIs → ↑ morbidity, ↑ mortality, and ↑ healthcare costs, partly by ↑ hospital stays.

HAIs are often caused by drug-resistant bacteria, for which appropriate diagnosis and treatment may not be available, or only at high cost. Hospitals serve as a selective environment for colonization with drug-resistant organisms that can later → disease, and/or are disseminated into the community by colonized patients on discharge from hospital.

Box 24.1 Types of HAI

- Bloodstream infections—associated with peripheral venous catheters, central venous catheters, and blood/blood product transfusions.
- Surgical site infections (SSIs) and wound infections.
- Urinary tract infections (UTIs)—usually catheter associated.
- Ventilator-associated pneumonia.
- Transfusion/injection-associated infection—esp. hepatitis B and C and HIV.
- Infectious diarrhoea, e.g. *Clostridium difficile* and *Norovirus*.
- Other examples and outbreaks, e.g. nosocomial TB transmission, SARS, and Ebola virus outbreaks.

Infection prevention and control (IPC)

IPC activities are key to combatting HAIs. The WHO's Infection Prevention and Control Global Unit (est. in 2016) emphasizes: (1) capacity building for IPC programmes, (2) surveillance of HAIs, (3) effective hand hygiene and injection safety, and (4) measures to combat antimicrobial resistance (AMR) and HAIs associated with invasive procedures (e.g. catheters, surgery) (http://www.who.int/infection-prevention/about/en/).

IPC activities are cost-effective, but it is often difficult to observe their impact in ↓ disease, esp. without adequate HAI surveillance and monitoring patient outcomes.

Key steps in implementing IPC

1. Instituting IPC programmes and IPC teams.
2. Implementing evidence-based guidelines.
3. IPC education and training.
4. HAI surveillance.
5. Audit of practice and feedback.
6. Appropriate staffing and bed spaces.
7. Adequate water, sanitation, and hand hygiene facilities.

In constrained resources these may be difficult to implement, and the evidence base for any specific intervention is often limited. Core IPC practices are listed in the following subsections.

Hand hygiene

HCWs' hands represent a potential route of transmission for many pathogens, and hand hygiene is simple.

- Wash hands with soap and water if they are visibly dirty, soiled with blood or body fluids, or *C. difficile* is a risk.
- In other contexts, alcohol-based hand rub is recommended.
- Handwashing requires sinks, soap, water supply, and a means of drying hands that will not re-contaminate them.
- Alcohol hand-rubs can be produced cheaply and locally (🔗 http://www.who.int/gpsc/5may/Guide_to_Local_Production.pdf).
  The WHO recommends 'Five moments for hand hygiene' (Fig. 24.1).

Personal protective equipment

- Gloves, aprons, surgical gowns, boots, masks, and protective eyewear are important, but may not be available.
- Gloves are not a substitute for proper hand hygiene.
- Surgical masks provide little protection against respiratory pathogens incl. TB.
- Expensive N95 masks offer limited benefit unless perfectly fitted.
- Cost-effective measures may include getting infectious patients to wear masks and designing healthcare facilities to maximize natural ventilation.

Isolation measures

Overcrowded, understaffed wards with >1 patient per bed can be normal in resource-poor settings, so effective IPC can be very difficult to implement.

Isolation rooms are a luxury many hospitals cannot afford, so 'cohorting' of patients with similar symptoms is often the best that can be achieved. This, in itself, can bring problems, e.g. putting patients with suspected TB together may mean that the most immunosuppressed HIV+ve individuals are then in close proximity to the most infectious smear +ve TB cases.

It is best to be pragmatic with the available facilities and resources.

Waste disposal

Disposal of needles and other sharps into safety sharps boxes is vital. Ensure proper disposal once sharps boxes are three-quarters full.

Waste should be segregated to red (highly infectious), yellow (infectious), and black (non-infectious) bags at the point of generation.

Infectious waste and sharps should be incinerated nearby, but >80% of waste generated by hospitals (e.g. packaging, food remains, paper) can go to municipal dumps—which is far cheaper.

Hospital hygiene

Maintenance of a clean hospital environment helps limit the spread of infections. Many pathogens are able to survive in the environment, and be transmitted to patients and staff. Regular, thorough cleaning of clinical areas incl. beds and adjacent surfaces with a suitable disinfectant, and regular laundry of bedding, are important.

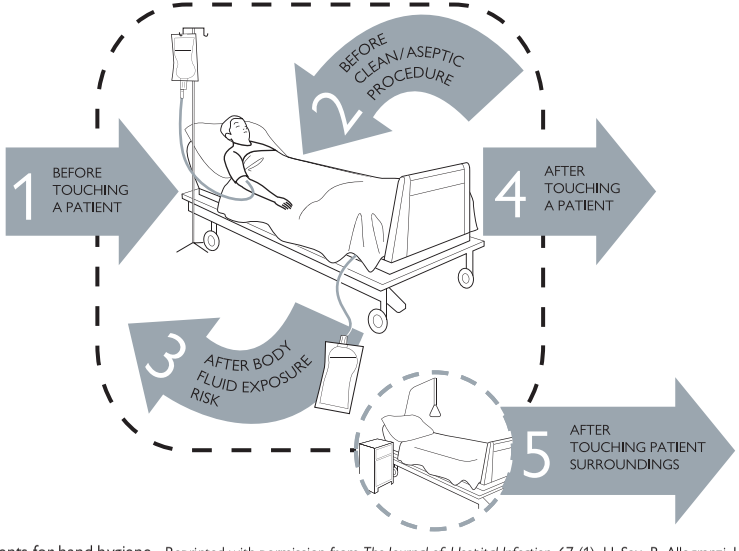

Fig. 24.1. Five moments for hand hygiene. Reprinted with permission from *The Journal of Hospital Infection*, 67 (1), H. Sax, B. Allegranzi. I. Uçkay, E. Larson, J. Boyce, and D. Pittet, 'My five moments for hand hygiene': a user-centred design approach to understand, train, monitor and report hand hygiene, pp. 9–21, Figure 2b, https://doi.org/10.1016/j.jhin.2007.06.004

Prevention of surgical site infections

SSIs are the commonest HAIs in resource-limited countries and surgical antibiotic prophylaxis helps ↓ SSIs. Surgical antibiotic prophylaxis should consist of a single preoperative dose of antibiotics(s) that covers the locally relevant pathogens/resistance, given <60min before skin incision. Repeat doses may be required for long procedures or if large volumes of blood are lost/replaced.

Routine postoperative antibiotics should be avoided; these are largely ineffective in preventing SSIs and ↑ drug resistance.

The choice of surgical antibiotic prophylaxis depends on the type of surgery, MRSA colonization status, and local resistance epidemiology. Use of checklists is also an important element of ensuring safe surgery (e.g. WHO checklist: http://www.who.int/patientsafety/safesurgery/ss_checklist/en/). Other measures in the perioperative period which ↓ SSI rates incl. adequate O_2, glucose control, and nutrition (WHO guidelines for the prevention of surgical site infection, 2016: http://www.who.int/infection-prevention/publications/ssi-prevention-guidelines/en/).

Injection safety

Contaminated injections → ~1.7 million HBV infections, ~310,000 HCV infections, and ~40,000 HIV infections/year. Syphilis, viral haemorrhagic fevers, and malaria can also be transmitted by injections. Consider whether an injection is necessary, ↓ the number of injections given (e.g. consider oral or no treatment if appropriate), and ensure injecting equipment is not reused and is appropriately disposed of. Safety-engineered, 'single use only' syringes and IV cannulas are available for little additional cost.

Use of HIV PEP after needlestick injuries is covered elsewhere (➲ Post-exposure prophylaxis following needlestick injuries, p. 124). All HCWs and laboratory staff should be fully immunized against HBV.

Blood/blood component transfusions

Blood/blood component transfusions are an important source of HAI, and the WHO recommends screening of blood products for HIV, HBV, HCV, syphilis (+/− for malaria, Chagas' disease, HTLV where appropriate). Blood packs that are poorly collected/stored inappropriately may become contaminated with bacteria, risking transfusion-associated sepsis. Balance the infectious risk and the potential benefits of each transfusion; ↓ blood/blood component transfusions conserves resources and ↓ risks to patients.

Nosocomial disease outbreaks

Hospital outbreaks of highly pathogenic viruses (e.g. Ebola, SARS) or bacteria (e.g. *Vibrio cholerae*) are uncommon, but can → high mortality. See sections on individual diseases for specific advice on outbreak management. Every hospital should have an outbreak emergency plan, incl. a method for communicating that an outbreak is taking place in the hospital and knowing when/who to ask for help.

More commonly, hospital outbreaks involve common viral/bacterial pathogens (e.g. *Norovirus*, drug-resistant bacteria) in high-risk patient groups or specialist wards, esp. ICUs, burns units, and neonatal care units. Effective control of these outbreaks is best achieved by vigorous enforcement of the IPC policies.

Principles of antimicrobial prescribing

Rational antimicrobial prescribing:

- Restricts the use of antimicrobials to patients who need them.
- Focuses on likely pathogens and resistance profile.
- ↓ side effects and perturbation of healthy microbiota.
- → the administration of antimicrobials for as short a duration as necessary to attain cure.
- Aims to ↑ patient benefit, ↓ patient harm, ↓ healthcare costs, and ↓ development of AMR. It is highly relevant in resource-poor settings where the choice of available antimicrobial drugs is limited and AMR prevalence is often high.

General principles of antimicrobial prescribing

- *Consider the clinical syndrome* (e.g. community- or healthcare-associated pneumonia, meningitis, UTI, etc.) and the common pathogens associated with this syndrome. Follow local/national/WHO guidelines if available.
- *Consider how unwell the patient is* and what the risks are of inappropriately narrow antimicrobial therapy. If the risks are high (e.g. death in septic shock, neurological impairment in meningitis), commence broad-spectrum empiric therapy with a view to narrowing when possible.
- *If facilities exist, take relevant specimens for culture/testing* (e.g. blood, urine, pus, respiratory specimens faeces, etc.) before starting antimicrobial therapy. Do not delay antimicrobial administration for the purposes of taking samples in patients who have severe infection (e.g. septic shock, meningitis); in these situations delay is associated with ↑ mortality. Consider any previous microbiological specimen results from your patient if available (e.g. MRSA colonization status).
- *Know the local epidemiology of antimicrobial resistance patterns for major pathogens.* These can differ according to geographic location, and change significantly over time.
- *Consider the most appropriate route.* Give IV antimicrobials for severe infections, and when GI absorption may be ↓ (e.g. vomiting). Some commonly used antimicrobials (e.g. ceftriaxone, gentamicin) cannot be given orally. Use oral antimicrobials in preference if there is no good indication for IV administration.
- *Consider allergies, drug interactions, renal/hepatic drug clearance, and side effects when making your antimicrobial choice*.
- *Reassess patients regularly and adjust/de-escalate depending on clinical response and culture results*. If in doubt, consult an infection specialist if available. Switching IV antimicrobials to oral formulations at 24–48h is often possible if the patient is improving. Avoid prolonging treatment unnecessarily.
- *Always document clinical indication, drug name, dose/route of administration, and review/stop date*.

Strategies to improve antimicrobial use

- Restricting antimicrobials and requiring senior/specialist approval for prescription of second- or third-line treatments—so they are reserved for patients who need them.
- Evidence-based guidelines for management of specific clinical syndromes (e.g. pneumonia, meningitis, soft tissue infections, etc.), accompanied by education around antimicrobial prescribing, audit, and feedback on prescribing practices.
- Establishing an antimicrobial stewardship team if feasible—incl. an infectious diseases physician or microbiologist and a pharmacist.
- Improving diagnostic services to assist prescribing decisions.
- ↓ pathogen transmission through immunization programmes and IPC interventions (e.g. hand hygiene).

Indications for antibiotics (= antibacterial drugs)

Indications for antibiotics include the following common clinical syndromes:

- Septic shock or signs of sepsis (➲ Sepsis, p. 678).
- Severe malaria—in which bloodstream infection may also be present (➲ Chapter 2).
- Pneumonia (➲ Pneumonia, p. 171), meningitis (➲ Acute bacterial meningitis, p. 392), and UTIs.
- Severe/complicated diarrhoea unless haemolytic uraemic syndrome is suspected.
- Skin and soft tissue infections, for which surgical management may also be required (e.g. abscesses, necrotizing fasciitis and gas gangrene).

Have a lower threshold for giving antibiotics to an immunosuppressed patient or those at the extremes of age.

Antibiotics are *not* indicated for specific treatment of the following:

- Colds.
- Influenza (antiviral therapy may be warranted).
- Uncomplicated diarrhoea and bloody diarrhoea if haemolytic uraemic syndrome is suspected.
- Non-severe malaria.
- Asymptomatic bacteriuria (except in pregnant women).

Single dose/short-term antibiotic prophylaxis is sometimes used:

- Surgical prophylaxis—dosing immediately preoperatively.
- ↓ transmission of certain pathogens (e.g. for close contacts of meningococcal meningitis).
- ↓ mother-to-child transmission of group B streptococci with penicillin or clindamycin.

Long-term antibiotic prophylaxis is sometimes used:

- ↓ opportunistic infections in HIV (➲ p. 83) and other immunosuppressed populations (e.g. trimethoprim–sulfamethoxazole).
- Penicillin prophylaxis for group A streptococci in rheumatic heart disease (and occasionally for recurrent group A streptococcal cellulitis).
- Penicillin prophylaxis in children with sickle cell disease or splenectomy.

Antimicrobial resistance

AMR is a global problem, esp. in resource-poor settings. The availability, quality, and use of antibiotics are frequently unregulated, and ↑ resistance in communities and hospitals, and pathogen transmission, are facilitated by poor sanitation and hygiene. Lack of resources, competing public health priorities, and under-recognition of the extent of the problem due to limited AMR surveillance means the response to AMR is often inadequate.

Healthcare facilities with resource-limited antibiotic formularies quickly reach their limits of treatment in the face of AMR. Inadequate or non-existent surveillance → poor understanding of the AMR problem.

Drug resistance in bacterial pathogens

Antibiotic exposure selects for resistant organisms, not only among pathogens, but also within human (esp. gut, skin, and nasal flora) and animal microbiota, and environmental reservoirs. Resistance determinants are often carried on mobile genetic elements (e.g. plasmids) and can be transmitted within and between species. These mobile genetic elements may carry multiple AMR genes, meaning that selective pressure exerted by the use of one class of antibiotic can select for multidrug resistance. Once resistance to all available antibiotics occurs, infections become untreatable.

The epidemiology of AMR is always changing, but recent problem pathogens highlighted by various national and international agencies include those in Box 24.2. The 'One Health' approach to the evolution and transmission of drug-resistant bacteria simultaneously considers the cycle of antimicrobial use, selection pressures, and the effects on humans, animals, and the environment.

Drug resistance in *Mycobacterium tuberculosis* (TB)

TB remains the leading infectious cause of death, and AMR is a major challenge, fuelled by improper treatment/poor compliance, intermittent drug supply, and unreliable drug quality. The proportion of cases of multidrug-resistant TB (MDR-TB; resistance to rifampicin and isoniazid) and extensively drug-resistant (XDR-TB; resistance to rifampicin, isoniazid, a fluoroquinolone, and an injectable aminoglycoside) is increasing. Accurate diagnosis of these was hampered by lack of TB culture in resource-poor settings, but rapid molecular diagnostic tests (e.g. Xpert MTB/RIF Ultra assay) have been useful. Novel drugs such as bedaquiline and delamanid have been developed for treating MDR/XDR-TB, but treatment regimens are long and often poorly tolerated.

Drug resistance in malaria

ACTs have been crucial to global malaria management strategies, and are now the first line for treatment of *Plasmodium falciparum* and chloroquine-resistant *P. vivax* malaria. Artemisinin resistance in *P. falciparum* → delayed parasite clearance, typically associated with certain *pfkelch13* (*k13*) gene mutations. However, multidrug resistance (delayed parasite clearance with artemisinins + ACT partner drug resistance) has emerged in the Greater Mekong Subregion, and there is significant concern that similar multidrug resistance will emerge in Africa.

Drug resistance in HIV

Current recommendations are that ART should be started in all adults (and considered for all children/adolescents) with HIV at any CD4 cell count. Resistance in HIV largely results from poor adherence to therapy. Pre-treatment resistance to first-line ART has ↑ steadily to >10% in some countries. The emergence of resistance in HIV reflects inadequate drug supply chains, access to testing and monitoring, and adherence to/tolerance of ART.

Box 24.2 Major drug-resistant bacteria

Methicillin-resistant Staphylococcus aureus (MRSA)

A global problem—prevalence in tropical countries often high. Phenotypic or molecular testing is needed to diagnose MRSA. Drug treatments (e.g. vancomycin) are often unavailable in resource-poor settings.

Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae

- Very common in resource-poor settings, with carriage rates of >50% in the community in SE Asia. ESBLs → resistance to third-generation cephalosporins.
- ESBL organisms often multidrug resistant; infections commonly require treatment with carbapenems (may not be available and → emergence of carbapenem-resistant organisms).

Carbapenem-resistant organisms (CROs)

Includes carbapenemase-producing Enterobacteriaceae (CPE), carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii*. CPE may carry transmissible carbapenemases (e.g. KPC, NDM, OXA-48). CROs are often multidrug resistant; there may be no effective treatment, or toxic, poorly tolerated drugs (e.g. colistin).

Vancomycin-resistant enterococci (VRE)

Often a problem in hospitalized, immunocompromised patients (e.g. haematology/oncology), and in those with previous antibiotic exposure. Daptomycin, linezolid, and lipoglycopeptides are possible drugs.

Multidrug-resistant typhoidal (S. typhi, S. paratyphi) and non-typhoidal Salmonella spp. (NTS)

Multidrug resistance (= resistance to ampicillin, trimethoprim–sulfamethoxazole, and chloramphenicol) is common in *S. typhi/paratyphi* and NTS. Quinolone resistance is common in parts of Asia and Africa, and ceftriaxone and azithromycin resistance can be mediated by the acquisition of ESBL or macrolide phosphotransferase genes.

Multidrug-resistant Neisseria gonorrhoeae

↑ resistance to ciprofloxacin, azithromycin, and third-generation cephalosporins → WHO recommends combination of ceftriaxone plus azithromycin.

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