OST OXFORD SPECIALTY TRAINING

Edited by
Elaine Jolly
Andrew Fry
Afzal Chaudhry

TRAINING IN MEDICINE

Oxford Specialty Training: Training in Medicine

Oxford Specialty Training: Training in Medicine

Edited by

Elaine Jolly

Specialist Registrar in Nephrology and General Internal Medicine
Department of Medicine
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Andrew Fry

Consultant in Nephrology and Acute Medicine
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Afzal Chaudhry

Chief Medical Information Officer
Consultant Physician
Associate Lecturer
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Series Editor

Matthew D. Gardiner

Specialty Trainee in Plastic Surgery
Imperial College London

Honorary Clinical Lecturer in Plastic Surgery
Kennedy Institute of Rheumatology
University of Oxford

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 2016

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2015956497

ISBN 978–0–19–923045–7

Printed in Italy by
L.E.G.O. S.p.A.

Contents

Detailed contents

Symbols and abbreviations

❗	warning
▶	important
↓	decreased
↑	increased
↔	normal
♂	male
♀	female
~	approximately
±	plus/minus
2,3-DPG	2,3-diphosphoglycerate
2D	two-dimensional
3D	three-dimensional
5ASA	5-aminosalicylic acid
α	alpha
A&E	accident and emergency department
A1AT	alpha-1 antitrypsin
AA	aplastic anaemia
AAA	abdominal aortic aneurysms
AAFB	acid and alcohol-fast bacilli
AASV	ANCA-associated systemic vasculitis
ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ABPI	ankle–brachial pressure index
ACA	anticentromere antibody
ACA	anterior cerebral artery
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ACL	anticardiolipin antibody
ACLE	acute cutaneous lupus erythematosus
ACLF	acute on chronic liver failure
ACR	albumin:creatinine ratio
ACS	acute coronary syndromes
ACS	abdominal compartment syndrome
ACTH	adrenocorticotrophic hormone
AD	Alzheimer dementia
AD	autosomal dominant
ADH	antidiuretic hormone
ADP	adenosine diphosphate
AE	atopic eczema
AED	antiepileptic drug
AF	atrial fibrillation
AHA	acquired haemophilia-A
AI	adrenal incidentaloma
AICA	anterior inferior cerebral artery
AIDS	acquired immunodeficiency syndrome
AIH	autoimmune hepatitis
AKI	acute kidney injury
ALCL	anaplastic large cell lymphoma
ALD	alcoholic liver disease
ALF	acute liver failure
ALL	acute lymphoblastic leukaemia
AMI	acute myocardial infarction
AML	acute myeloid leukaemia
AN	acanthosis nigricans
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
aO_2	arterial oxygen content
APC	activated protein C
APD	automated peritoneal dialysis
aPL	antiphospholipid antibody
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AR	autosomal recessive
AR	aortic regurgitation
ARAS	ascending reticular activating system
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
ARF	cute renal failure
ARR	absolute risk reduction
ART	antiretroviral therapy
AS	Angelman syndrome
AS	ankylosing spondylitis
ASA	anterior spinal artery
ASD	atrial septal defect
ASH	alcoholic steatohepatitis
AT	antithrombin
ATD	antithyroid drug
ATG	antithymocyte globulin
ATIN	acute interstitial nephritis
ATLL	adult T-cell leukaemia/lymphoma
ATP	adenosine triphosphate
AV	atrioventricular
AVF	arteriovenous fistula
AVM	arteriovenous malformation
AVNRT	atrioventricular nodal re-entry tachycardia
AVP	arginine vasopressin
AVRT	atrioventricular re-entry tachycardia
AWS	alcohol withdrawal syndrome
AXR	abdominal X-ray
AZT	zidovudine
β	beta
B2M	beta-2-microglobulin
BAL	bronchoalveolar lavage
BASHH	British Association for Sexual Health and HIV
BBB	bundle branch block
BBBB	blood–brain barrier breakdown
BBV	blood-borne virus
BCG	Bacillus Calmette–Guérin
BD	twice a day
BDA	Blackman–Diamond anaemia

BHIVA	British HIV Association
BHS	British Hypertension Society
BIPAP	bilevel positive airway pressure
BL	Burkitt lymphoma
BMD	bone mineral density
BMI	body mass index
BNF	*British National Formulary*
BP	blood pressure
B-PLL	B-prolymphocytic leukaemia
BPPV	benign paroxysmal positional vertigo
C&S	culture and sensitivity
CA	cancer antigen
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
CAL	café-au-lait
cANCA	cytoplasmic antineutrophil cytoplasmic antibody
CAPD	continuous ambulatory peritoneal dialysis
CAS	cold agglutinin disease
CASS	continuous aspiration of subglottic secretions
CBD	corticobasal degeneration
CBG	cortisol binding globulin
CCP	cyclic citrullinated peptide
CCU	critical care unit
CD	cluster of differentiation
CD	Cushing disease
CDAD	Clostridium difficile-associated diarrhoea
CDK	cyclin-dependent kinase
CEA	carcinoembryonic antigen
CFU	colony-forming unit
CGH	comparative genomic hybridization
CHF	chronic heart failure
CHL	classical Hodgkin lymphoma
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone
CHOP	carbohydrate
CIDP	chronic inflammatory demyelinating polyneuropathy
CIN	contrast-induced nephropathy
CIN	chronic interstitial nephritis
CK	creatine kinase
CLL	chronic lymphocytic leukaemia
CLP	common lymphoid precursor
CML	chronic myeloid leukaemia
CMML	chronic myelomonocytic leukaemia
CMP	common myeloid precursor
CMT	Charcot–Marie–Tooth
CMV	Cytomegalovirus
CN	cranial nerve
CNS	central nervous system
CO	carbon monoxide
CO	cardiac output
CO_2	carbon dioxide
COHb	carboxyhaemoglobin
CoNS	coagulase-negative staphylococci
CoW	Circle of Willis
COX	cyclo-oxygenase
CPAP	continuous positive airway pressure
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
CR	complete remission
CRBSI	catheter-related bloodstream infection
CRC	colorectal cancer
CrCl	creatinine clearance
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CRP	complement receptor
CS	Cushing syndrome
CS	carcinoid syndrome
CSA	ciclosporin
CSF	cerebrospinal fluid
CSII	continuous subcutaneous insulin infusion
CSM	Committee on Safety of Medicines
CSS	Churg–Strauss syndrome
CT	computed tomography
CTPA	computed tomography pulmonary angiogram
CV	cardiovascular
CVA	cerebrovascular accident
CVC	central venous catheter
CVID	common variable immunodeficiency
CVP	central venous pressure
CVS	chorionic villus sample
CVVH	continuous veno-venous haemofiltration
CVVHDF	continuous veno-venous diafiltration
CXR	chest X-ray
DAD	diffuse alveolar damage
DAT	direct antiglobulin test
DBP	diastolic blood pressure
DC	dyskeratosis congenita
DCM	dilated cardiomyopathy
dcSS	diffuse cutaneous systemic sclerosis
DDx	differential diagnosis
DeE	dementia elderly
DEET	diethyl toluamide
DFS	disease-free survival
DG	diglyceride
DHAP	cisplatin, cytarabine, and dexamethasone
DHEAS	dehydroepiandrosterone sulphate
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DLB	dementia with Lewy bodies
DLBCL	diffuse large B-cell lymphoma
DLE	discoid lupus erythematosus
DM	diabetes mellitus
DN	diabetic nephropathy
DNAR	do not attempt resuscitation
DO_2	oxygen delivery
dsDNA	double stranded deoxyribonucleic acid
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
DXA	dual-energy X-ray absorptiometry
EAA	extrinsic allergic alveolitis
EAS	ectopic ACTH syndrome
EBUS	endobronchial ultrasound
EBV	Epstein–Barr virus

ECG	electrocardiogram
ECM	extracellular matrix
ECMO	extracorporeal membrane oxygenation
ED	emergency department
ED	erectile dysfunction
EDS	Ehlers–Danlos syndrome
EDTA	ethylenediaminetetraacetic acid
EDV	end-diastolic volume
EEG	electroencephalogram
EGDT	early goal-directed therapy
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EM	erythema multiforme
EMA	European Medicines Agency
EMG	electromyogram
EMI	elderly mentally infirm
EMR	endoscopic mucosal resection
ENA	extractable nuclear antigen
ENS	enteric nervous system
ENT	ear, nose, and throat
EPO	erythropoietin
ERCP	endoscopic retrograde cholangiopancreatography
ESBL	extended-spectrum beta-lactamase
ESR	erythrocyte sedimentation rate
ESRF	end-stage renal failure
ESV	end-systolic volume
ET	essential thrombocythaemia
ET	endotracheal tube
FA	Fanconi anaemia
FA	fatty acid
FAB	French–American–British
FBC	full blood count
FCHL	familial combined hyperlipidaemia
FDA	Food and Drug Administration
FDG	2-fluoro-2-deoxy-D-glucose
FEV1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FHH	familial hypocalciuric hypercalcaemia
FISH	fluorescent in situ hybridization
FLAIR	fluid attenuated inversion recovery
FNA	fine needle aspiration
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FVC	forced vital capacity
γ	gamma
G6PD	glucose-6-phosphate dehydrogenenase
GABA	gamma-aminobutyric acid
GBM	glomerular basement membrane
GBS	Guillain–Barré syndrome
GCA	giant cell arteritis
GCS	Glasgow Coma Scale
G-CSF	granulocyte colony stimulating factor
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GH	growth hormone
GHRH	growth hormone-releasing hormone
GHS	growth hormone secretagogue
GI	gastrointestinal
GM	grey matter
GM-CSF	granulocyte macrophage colony-stimulating factor
GN	glomerulonephritis
GnRH	gonadotropin-releasing hormone
GORD	gastro-oesophageal reflux disease
GP	glycoprotein
GPI	glycosylphosphatidylinositol
GTN	glyceryl trinitrate
GVHD	graft-versus-host disease
H&E	haematoxylin and eosin
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HbA1c	glycated haemoglobin
HBC	hepatitis B virus
HBcAG	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBGM	home blood glucose monitoring
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular cancer
hCG	human chorionic gonadotropin
HCL	hairy cell leukaemia
Hct	haematocrit
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDM	house dust mite
HDU	high dependency unit
HDV	hepatitis D virus
HE	hereditary elliptocytosis
HER	human epidermal growth factor receptor
HEV	hepatitis E virus
HFOV	high-frequency oscillation ventilation
HH	hereditary haemochromatosis
HHS	hyperosmolar hyperglycaemic state
HIGM	X-linked hyper IgM
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HLA	human leucocyte antigen
HMSN	hereditary motor and sensory neuropathy
HMW	high molecular weight
HMWK	high-molecular-weight kininogen
HNPCC	hereditary non-polyposis colorectal cancer
HNPP	hereditary neuropathy and liability to pressure palsies
HOCM	hypertrophic obstructive cardiomyopathy
HPA	Health Protection Agency
HPA	hypothalamic–pituitary–adrenal
HPV	human papilloma virus
HRCT	high-resolution computed tomography
HRS	Hodgkin and Reed/Sternberg
HRS	hepatorenal syndrome

HS	hereditary spherocytosis
HSC	hepatic stellate cell
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplantation
HSE	herpes simplex encephalitis
HSP	Henoch–Schönlein purpura
HSV	herpes simplex virus
HTLV	human T-cell leukaemia virus
HUS	haemolytic uraemic syndrome
IAH	intra-abdominal hypertension
IAT	indirect antiglobulin test
IBD	inflammatory bowel disease
IBN	inclusion body myositis
IBS	irritable bowel syndrome
ICB	intracerebral bleed
ICD	implantable cardioverter defibrillators
ICP	intracranial pressure
ICU	intensive care unit
IDF	International Diabetes Federation
IDSA	Infectious Diseases Society of America
IDT	intradermal testing
IE	infective endocarditis
IF	intrinsic factor
IF	immunofluorescence
IF	intrinsic factor
IFN	interferon
IFRT	involved field radiotherapy
Ig	immunoglobulin
IgAN	immunoglobulin A nephropathy
IGF	insulin-like growth factor
IGT	impaired glucose tolerance
IHA	immune haemolytic anaemia
IHD	ischaemic heart disease
IIH	idiopathic intracranial hypertension
IJV	internal jugular vein
IL	interleukin
IM	intramuscular
INO	internuclear opthalmoplegia
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IPI	International Prognostic Index
IPSS	international prognostic scoring system
ITP	idiopathic thrombocytopenic purpura
ITT	insulin tolerance test
IV	intravenous
IVCD	intraventricular conduction defect
IVDU	intravenous drug use
IVIG	intravenous immunoglobulin
Ix	investigation
JGA	juxtaglomerular apparatus
JME	juvenile myoclonic epilepsy
JVP	jugular venous pulse/pressure
KF	Kayser–Fleischer
KS	Kaposi sarcoma
KUB	kidneys/ureter/bladder
LA	lupus anticoagulant
LA	left atrial/atrium
LACS	lacunar syndrome
LBBB	left bundle branch block
LBC	liquid-based cytology
lcSS	limited cutaneous systemic sclerosis
LCV	leucocytoclastic vasculitis
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LEMS	Lambert–Eaton myasthenic syndrome
LFT	liver function test
LH	luteinizing hormone
LIDCO	lithium dilution cardiac output
LMN	lower motor neurone
LMWH	low-molecular-weight heparin
LOC	loss of consciousness
LP	lumbar puncture
LP	lichen planus
LQTS	long QT syndrome
L-T3	levo-triiodothyronine
L-T4	levo-thyroxine
LTG	lamotrigine
LUQ	left upper quadrant
LV	left ventricular/ventricle
LVD	left ventricular dysfunction
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVSD	left ventricular systolic dysfunction
MAC	*Mycobacterium avium* complex
MAG3	mercaptoacetyltriglycine
MAHA	microangiopathic haemolytic anaemia
MAI	*Mycobacterium avium-intracellulare*
MALT	mucosa-associated lymphoid tissue
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MCA	middle cerebral artery
MCD	minimal change disease
MCGN	mesangiocapillary glomerulonephritis
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCI	mass casualty incident
MCL	mantle cell lymphoma
MCTD	mixed connective tissue disease
MDR	multidrug-resistant
MDR-TB	multidrug-resistant tuberculosis
MDS	myelodysplastic syndromes
MDS-U	myelodysplastic syndrome unclassified
MDT	multidisciplinary team
MELD	model for end-stage liver disease
MEN	multiple endocrine neoplasia
MF	mycosis fungoides
MG	monoglyceride
MG	myasthenia gravis
MGUS	monoclonal gammopathy of uncertain significance
MHC	major histocompatibility complex
MHC	major histocompatibility complex

MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIBG	metaiodobenzylguanidine
MIC	minimum inhibitory concentration
MIMMS	major incident management and support
MIT	multiple injection therapy
MLF	medial longitudinal fasciculus
MLPA	multiplex ligation-dependent probe amplification
MM	multiple myeloma
MMF	mycophenolate mofetil
MMSE	Mini Mental State Examination
MND	motor neurone disease
MND	membranous nephropathy
MOF	multi-organ failure
MP	mercaptopurine
MR	mitral regurgitation
MR	mineralocorticoid receptor
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MRV	magnetic resonance venography
MS	multiple sclerosis
MSM	men who have sex with men
MSSA	methicillin-sensitive *Staphylococcus aureus*
MTB	*Mycobacterium tuberculosis*
MTCT	mother-to-child transmission
mtDNA	mitochondrial DNA
MV	mitral valve
MVO_2	myocardial oxygen demand
NAC	N-acetylcysteine
Nad	noradrenaline
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NBM	nil by mouth
NEA	non-epileptic attack
NET	neuroendocrine tumour
NF	neurofibromatosis
NHL	non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NINDS	National Institute of Neurological Disorders and Stroke
NIV	non-invasive ventilation
NK	natural killer
NL	necrobiosis lipoidica
NMDA	N-methyl-D-aspartate
NNRTI	non-nucleoside reverse transcriptase inhibitor
NNT	number needed to treat
NO	nitric oxide
NPV	negative predictive value
NREM	non-rapid eye movement
NRTI	nucleoside reverse transcriptase inhibitor
NS	nephrotic syndrome
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NSF	national service framework
NSTEACS	non-ST elevation acute coronary syndromes
NSTEMI	non-ST elevation myocardial infarction
NTM	non-tuberculous mycobacteria
NYHA	New York Heart Association
O/E	on examination
O_2	oxygen
OA	osteoarthritis
OCP	oral contraceptive pill
OD	once a day
OGTT	oral glucose tolerance test
OHGA	oral hypoglycaemic agent
OR	odds ratio
OS	overall survival
PAC	pulmonary artery catheter
$PaCO_2$	arterial partial pressure of carbon dioxide
PACS	partial anterior circulation syndrome
PAH	pulmonary arterial hypertension
PAMP	pathogen-associated molecular pattern
PAN	polyarteritis nodosa
PaO_2	arterial partial pressure of oxygen
PAR	patient at risk
PAS	periodic acid–Schiff
PBC	primary biliary cirrhosis
PBP	penicillin binding protein
PCA	posterior cerebral artery
PCH	paroxysmal cold haemoglobinuria
PCI	percutaneous coronary intervention
PCOS	polycystic ovarian syndrome
PCP	Pneumocystis pneumonia
PCR	polymerase chain reaction
PCT	porphyria cutanea tarda
PCWP	pulmonary capillary wedge pressure
PD	Parkinson disease
PD	peritoneal dialysis
PDT	photodynamic therapy
PEA	pulseless electrical activity
PEEP	positive end- expiratory pressure
PEFR	peak expiratory flow rate
PEG	percutaneous endoscopic gastroscopy
PEP	post-exposure prophylaxis
PET	positron emission tomography
PF	platelet factor
PFS	progression-free survival
Ph	Philadelphia
PHA	primary hyperaldosteronism
PHG	portal hypertensive gastropathy
PHY	phenytoin
PI	protease inhibitor
PICA	posterior inferior cerebral artery
PiCCo	pulse-induced contour cardiac output
PK	pyruvate kinase
PKU	phenylketonuria
PMC	pseudomembranous colitis
PM	primary myelofibrosis
PML	progressive multifocal leucoencephalopathy
pmp	per million population

PMR	polymyalgia rheumatica
PN	parenteral nutrition
PNES	psychogenic non-epileptic seizures
PNH	paroxysmal nocturnal haemoglobinuria
PO	*per os* (orally)
pO_2	partial pressure of oxygen
POCS	posterior circulation syndrome
POMC	pro-opiomelanocortin
PPI	proton-pump inhibitor
PPMS	primary progressive multiple sclerosis
PPRF	paramedian pontine reticular formation
PPV	positive predictive value
PR	per rectum (rectally)
PSA	prostate-specific antigen
PsA	psoriatic arthritis
PSA	prostate-specific antigen
PSC	primary sclerosing cholangitis
PSP	progressive supranuclear palsy
PT	prothrombin time
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disorder
PUD	peptic ulcer disease
PUJ	pelviureteric junction
PUO	pyrexia of unknown origin
PUVA	psoralen and ultraviolet A
PV	polycythaemia vera
PVS	persistent vegetative state
PWS	Prader–Willi syndrome
Px	prognosis
QID	four times a day
QOF	Quality Outcome Framework
RA	rheumatoid arthritis
RA	refractory anaemia
RA	right atrial/atrium
RAA	renin–angiotensin–aldosterone
RAEB	refractory anaemia with excess of blasts
RAI	radioiodine
RARS	refractory anaemia with ringed sideroblasts
RAST	radioallergosorbent test
RBBB	right bundle branch block
RBC	red blood cell
RCC	renal cell carcinoma
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
RCMD	refractory cytopenia with multilineage dysplasia
RCT	randomized controlled trial
RCUD	refractory cytopenias with unilineage dysplasia
RDW	red cell distribution width
ReA	reactive arthritis
REM	rapid eye movement
RF	rheumatoid factor
RhF	rheumatoid factor
RIC	reduced intensity conditioning
RIPA	ristocetin-induced platelet aggregation
RN	refractory neutropenia
ROC	receiver operating characteristic
RPE	retinal pigment epithelium
RPGN	rapidly progressive glomerulonephritis
RR	relative risk
RRT	renal replacement therapy
RSV	respiratory syncytial virus
RT	refractory thrombocytopenia
RTA	renal tubular acidosis
rTPA	recombinant tissue plasminogen activator
RT-PCR	reverse transcription polymerase chain reaction
RUQ	right upper quadrant
RV	residual volume
RV	right ventricular/ventricle
Rx	treatment
SA	sinoatrial
SAGH	subclinical autonomous glucocorticoid hypersecretion
SAH	subarachnoid haemorrhage
SARS	severe acute respiratory syndrome
SBP	systolic blood pressure
SC	subcutaneous
SCC	squamous cell carcinoma
SCD	sudden cardiac death
SCLC	small cell lung cancer
SCLE	subacute cutaneous lupus erythematosus
SD	standard deviation
SHBG	sex hormone binding globulin
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIRS	systemic inflammatory response syndrome
SJS	Stevens–Johnson syndrome
SK	seborrhoeic keratosis
SLE	systemic lupus erythematosus
SLR	straight leg raise
SOB	shortness of breath
SOL	space-occupying lesion
SPD	storage pool disease
SPECT	single-photon emission computed tomography
SPT	skin prick testing
SS	systemic sclerosis
SS	Sézary syndrome
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin re-uptake inhibitor
SST	short Synacthen® test
STEMI	ST-elevation myocardial infarction
SUDEP	sudden unexplained death in epilepsy
SVC	superior vena cava
SVCO	superior vena cava obstruction
SVR	systematic vascular resistance
SVT	supraventricular tachycardia
Sx	symptoms
$t_{1/2}$	half-life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TACS	total anterior circulation syndrome
TAVI	transcutaneous aortic valve implantation
TB	tuberculosis

TBG	thyroid binding globulin
TBI	traumatic brain injury
Tc	technetium
TCA	tricyclic antidepressant
TCC	transitional cell carcinoma
TEDS	thromboembolic deterrent stockings
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TfR	transferrin receptor
TFT	thyroid function test
TG	triglyceride
TG	thyroglobulin
Th	T helper
TIA	transient ischaemic attack
TIBC	total iron binding capacity
TID	three times a day
TIPSS	transjugular intrahepatic portosystemic stent shunt
TKI	tyrosine kinase inhibitor
TLC	total lung capacity
TLCO	transfer factor of carbon monoxide
TNF	tumour necrosis factor
TOE	transoesophageal echocardiography
TPMT	thiopurine S-methyltransferase
TPMT	thiopurine methyl transferase
TPN	total parenteral nutrition
TPO	thrombopoietin
TPO	thyroid peroxidase
TR	tricuspid regurgitation
TRAb	TSH receptor antibody
TRH	thyrotropin-releasing hormone
TRM	transplant-related mortality
TSC	tuberous sclerosis complex
TSH	thyroid stimulating hormone
TSS	toxic shock syndrome
TTE	transthoracic echocardiography
TTP	thrombotic thrombocytopenic purpura
TZD	thiazolidinedione
U&Es	urea and electrolytes
UC	ulcerative colitis
UFH	unfractionated heparin
UMN	upper motor neurone
UO	urinary output
UPD	uniparental disomy
URTI	upper respiratory tract infection
USS	ultrasound scan
UTI	urinary tract infection
UV	ultraviolet
V/Q	ventilation/perfusion
VA	alveolar ventilation
VAP	ventilator-associated pneumonia
VATS	video-assisted thoracoscopic
VC	vital capacity
Vd	volume of distribution
VDLD	very low-density lipoprotein
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
VF	ventricular fibrillation
VHF	viral haemorrhagic fever
VILI	ventilator-induced lung injury
vO_2	venous oxygen content
VOR	vestibulo-ocular reflex
VPA	valproate
VRE	vancomycin-resistant enterococci
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VWD	von Willebrand disease
VWF	von Willebrand factor
VZV	varicella zoster virus
WBC	white blood cell
WCC	white cell count
WG	granulomatosis with polyangiitis (Wegener)
WHO	World Health Organization
WM	Waldenström macroglobulinaemia
WM	white matter
WPW	Wolff–Parkinson–White
XLA	X-linked agammaglobulinaemia
XP	xeroderma pigmentosum
ZF	zona fasciculata
ZG	zona glomerulosa
ZN	Ziehl–Neelsen
ZR	zona reticularis

Contributors

Victoria Allgar
Senior Lecturer in Medical Statistics
Hull and York Medical School/Health Sciences
University of York
York, UK

Anand Kumar Annamalai
Speciality Registrar in Endocrinology
Metabolic Research Laboratories
Wellcome Trust-MRC Institute of Metabolic Science
Addenbrooke's Hospital
Cambridge Biomedical Campus
Cambridge, UK

John Martin Bland
Professor of Health Statistics
Department of Health Sciences
University of York
York, UK

Timothy J Burton
Clinical Pharmacology
University of Cambridge
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Aristeidis Chaidos
Consultant Haematologist
Imperial College Healthcare NHS Trust
London, UK

Afzal N Chaudhry
Chief Medical Information Officer
Consultant Physician
Associate Lecturer
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

John Connelly
Wellcome Trust Senior Clinical Fellow and Consultant Hepatologist
MRC Centre for Inflammation Research
Queen's Medical Research Institute
University of Edinburgh
Edinburgh, UK

Paul A Corris
Professor of Thoracic Medicine and Honorary Consultant
Institute of Cellular Medicine
Newcastle University and Department of Respiratory Medicine
Freeman Hospital
Newcastle upon Tyne, UK

Francesco Dazzi
Professor of Regenerative and Haematological Medicine
KHP Lead for Cellular Therapies
King's College
London, UK

Anthony De Soyza
Senior Lecturer and Honorary Consultant
Institute of Cellular Medicine
Newcastle University and Department of Respiratory medicine
Freeman Hospital
Newcastle upon Tyne, UK

Giles Dunnill
Consultant Dermatologist
Department of Dermatology
Bristol Royal Infirmary
Bristol, UK

Spencer Ellis
Consultant Rheumatologist and General Physician
Department of Rheumatology
East and North Herts NHS Trust
Lister Hospital
Stevenage, UK

Nikos Evangelou
Division of Neurosciences
Queen's Medical Centre
Nottingham University Hospitals
University of Nottingham
England, UK

Professor TJ Evans
Institute of Infection, Immunity and Inflammation
University of Glasgow
Glasgow, UK

John Forrester
Section of Immunology and Infection
Division of Applied Medicine
School of Medicine and Dentistry
Institute of Medical Science, Foresterhill
University of Aberdeen
Scotland, UK
and
Ocular Immunology Program
Centre for Ophthalmology and Visual Science
The University of Western Australia
Australia
and
Centre for Experimental Immunology
Lions Eye Institute
Nedlands, Australia

Andrew Fry
Consultant in Nephrology and Acute Medicine
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Christopher P Gilmore
Department of Neurology
Queens Medical Centre NHS Trust
Nottingham University Hospitals
Nottingham, UK

Paul A Glynne
Consultant Physician
University College London NHS Foundation Trust
London, UK

Eleanor Gurnell
Consultant Diabetologist
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Mark Gurnell
Clinical SubDean
University of Cambridge School of Clinical Medicine
Senior Lecturer in Endocrinology
and
Honorary Consultant Physician
University of Cambridge
and
Metabolic Research Laboratories
Wellcome Trust-MRC Institute of Metabolic Science
Addenbrooke's Hospital
Cambridge Biomedical Campus
Cambridge, UK

Neil Henderson
Wellcome Trust Senior Clinical Fellow and Consultant Hepatologist
MRC Centre for Inflammation Research
Queen's Medical Research Institute
University of Edinburgh
Edinburgh, UK

David CJ Howell
Divisional Clinical Director
Critical Care Unit
University College London NHS Foundation Trust
London, UK

John Iredale
Regius Professor of Medical Science
MRC Centre for Inflammation Research
Queen's Medical Research Institute
University of Edinburgh
Edinburgh, UK

Elaine C Jolly
Specialist Registrar in Nephrology and General Internal Medicine
Department of Medicine
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Dinakantha Kumararatne
Consultant Clinical Immunologist
Immunology Department
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Jeffrey Lee
Consultant Rheumatologist & General Physician
Department of Rheumatology
Barnet Hospital
Royal Free Foundation NHS Trust
Hertfordshire, UK

John McMurray
Professor of Medical Cardiology
Institute of Cardiovascular & Medical Sciences
University of Glasgow
and
Honorary Consultant Cardiologist
Queen Elizabeth University Hospital
Glasgow, UK

Claire L Meek
Metabolic Physician
Metabolic Research Laboratories
Wellcome Trust-MRC Institute of Metabolic Science
Addenbrooke's Hospital
Cambridge Biomedical CampusCambridge, UK

Agnieszka Michael
Consultant Medical Oncologist
Royal Surrey County Hospital
and
Senior Lecturer
University of Surrey
Surrey, UK

Brian Murphy
Consultant Cardiologist
Queen Elizabeth University Hospital
Glasgow, UK

Claire Nicholl
Consultant Geriatrician
Department of Medicine for the Elderly
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Hardev Pandha
Professor of Medical Oncology
Targeted Cancer Therapy, Faculty of Health and Medical Sciences
University of Surrey
Guildford, UK

Dayangku Siti Nur Ashikin Pengiran Tengah
Consultant Neurologist
Neurology Division
Raja Isteri Pengiran Anak Saleha Hospital
Bandar Seri Begawan
Brunei

Andrew Powlson
Clinical Research Associate and Honorary Specialist Registrar
Metabolic Research Laboratories
Institute of Metabolic Science
University of Cambridge
Addenbrooke's Hospital
Cambridge Biomedical Campus Cambridge, UK

Rachel Quail
Consultant in Acute Medicine
East and North Herts NHS Trust
Lister Hospital
Stevenage, UK

Shefali Rajpopat
Consultant Dermatologist
Barts Health NHS Trust
London, UK

Kate Relph
Research Fellow
Targeted Cancer Therapy
Faculty of Health and Medical Sciences
University of Surrey
Guildford, UK

Paul Robertson
Specialty Registrar in Medical Microbiology
Department of Microbiology
Glasgow Royal Infirmary
Glasgow, UK

Anand Saggar
Consultant in Clinical Genetics
St George's University of London
London, UK

Jack Satsangi
Professor of Gastroenterology
University of Edinburgh
Edinburgh, UK

Suranjit Seneviratne
Consultant in Clinical Immunology and Allergy
Department of Clinical Immunology and UCL Centre for Immunodeficiency
Institute of Immunity and Transplantation
Royal Free Hospital
London, UK

Jonathan Silverman
Honorary Visiting Senior Fellow
School of Clinical Medicine
University of Cambridge
Cambridge, UK

Sumeet Singal
Consultant Neurologist
Queen's Medical Centre
Nottingham University Hospitals
Nottingham, UK

Derek Soon
Consultant Neurologist
National University Health System
Singapore, Singapore
and
Undergraduate Education Director for Medicine
Yong Loo Lin School of Medicine
National University of Singapore
Singapore, Singapore

Chris Strey
Facharzt Innere Medizin
Spez. Endokrinologie
eSwiss Medical Center
St. Gallen, Switzerland

Ravi Suchak
Department of Dermatology
Basildon University Hospital
Essex, UK

Emma Tallantyre
Post-CCT Research Fellow
Department of Clinical Neurology
University Hospital of Wales
Cardiff, UK

Jennifer Thomson
Consultant in Clinical Genetics
Leeds Teaching Hospitals NHS Trust
Chapel Allerton Hospital
Leeds, UK

Antoinette Tuthill
Consultant Endocrinologist and Lecturer
Cork University Hospital
Cork, Ireland

Stephen Wallis
Consultant Geriatrician
Department of Medicine for the Elderly
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

David Watts
Gastroenterologist and Clinical Lead
Gastrointestinal Unit
NHS Forth Valley
Forth Valley Royal Hospital
Larbert, UK

Robin AP Weir
Department of Cardiology
Hairmyres Hospital
Scotland, UK

Ian B Wilkinson
Professor of Therapeutics
Department of Medicine, EMIT Division
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Lisa C Willcocks
Consultant Nephrologist
Department of Medicine
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Graeme J Williams
Consultant Medical Ophthalmologist
Gartnavel General Hospital
Glasgow, UK

Katie Wood
Consultant Clinical Oncologist
Royal Surrey County Hospital
Guildford, UK
and
Clinical Oncologist
The Royal Surrey County Hospital NHS Foundation Trust
Surrey, UK

Chapter 1

Acute medical emergencies and practical procedures

1.1 Cardiorespiratory arrest

Definitions

- Respiratory arrest = lack of spontaneous respiratory effort.
- Cardiac arrest = absence of effective cardiac output.

Within 3 minutes of cardiorespiratory arrest, cerebral hypoxia develops resulting in brain damage, necessitating urgent cardiopulmonary resuscitation (CPR) and restoration of circulation where possible.

Presentation

Identified in patients who are unconscious, apnoeic, and with absent central pulses (carotid and/or femoral pulses).

Basic life support

Aiming to maintain adequate ventilation and circulation to preserve cerebral perfusion (Fig. 1.1).

Management

- Ensure personal safety in approach to patient.
- Shout for help.
- Check patient response.
- Turn patient onto their back.
- Open airway using head tilt and chin lift—use C-spine precautions if at risk of injury.
- Check airway—foreign body/debris (remove with forceps/suction).
- Look, listen, and feel for respiration whilst checking carotid pulsation—no longer than 10 seconds.
- If no sign of life, no respiratory effort, and no pulse: call cardiac arrest team.
- Commence CPR immediately (instigate if any doubt).
- 30 chest compressions followed by 2 ventilations.
- Hand position for chest compressions is the middle of the lower half of the sternum.
- Depth of 4–5cm with a rate of 100/minute.
- A palpable pulse should not be used to guide effectiveness of compressions.
- Ventilation (aiming inspiratory phase of 1 second) through pocket mask if a bag mask not immediately available—mouth-to-mouth if no adjunctive equipment available.
- If ventilation not possible or contraindicated if no equipment available (corrosives/poisons), continue uninterrupted chest compressions.
- Once defibrillator arrives immediately place pads/electrodes in position.
- Respiratory arrest only—ventilate, checking for carotid pulsation every 10 breaths.

Advanced life support

Provides a structured algorithm to follow in the case of cardiac arrest to facilitate treatment with the aim of restoring cardiac output (Fig. 1.2).

Improved survival has been shown for early defibrillation of shockable rhythms and effective CPR.

Shockable rhythms: ventricular fibrillation/tachycardia (VF/VT)

- Commonest rhythm seen in adult cardiac arrest—may be preceded by cardiac history or other arrhythmia.

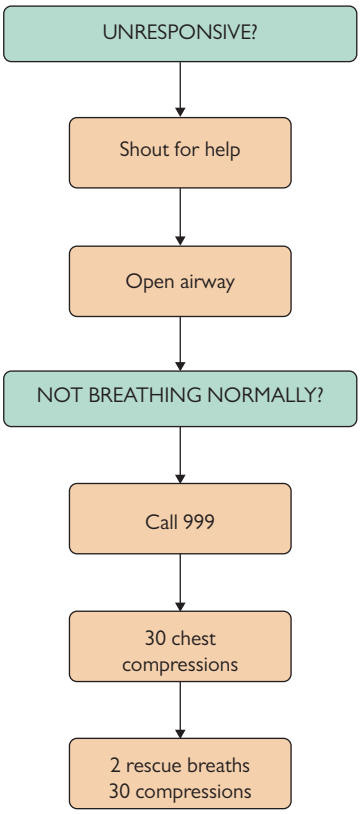


Fig. 1.1 Adult basic life support algorithm.
Reproduced with the kind permission of the Resuscitation Council (UK).

Management

- As for basic life support.
- In the case of witnessed and monitored cardiac arrest a precordial thump may be attempted—deliver a quick, sharp, recoiled impact to the lower half of the sternum from approximately 20cm.
- Confirmation of rhythm.
- Immediate defibrillation with 1 shock 150J biphasic (360J monophasic).
- Immediately resume chest compressions at 30:2.
- Continue CPR for 2 minutes.
- Establish IV access and consider intubation.
- Check monitor for rhythm.
- Persistent VF/VT: 1 shock 150J biphasic, with immediate recommencement of CPR for 2 minutes.
- Check monitor for rhythm.
- Persistent VF/VT: give 1mg IV adrenaline immediately followed by 1 shock (150J biphasic) and resumption of CPR for 2 minutes.
- Persistent VF/VT: give amiodarone 300mg IV immediately followed by 1 shock (150J) and commencement of CPR for 2 minutes.
- Continue to give further shocks if persistent VF/VT every 2 minutes.
- 1mg IV adrenaline prior to alternate shocks.
- Do not check for a pulse after delivery of a shock as this delays effective cardiac compressions and risks further myocardial damage.
- Drugs given should be flushed through with 20mL normal saline.

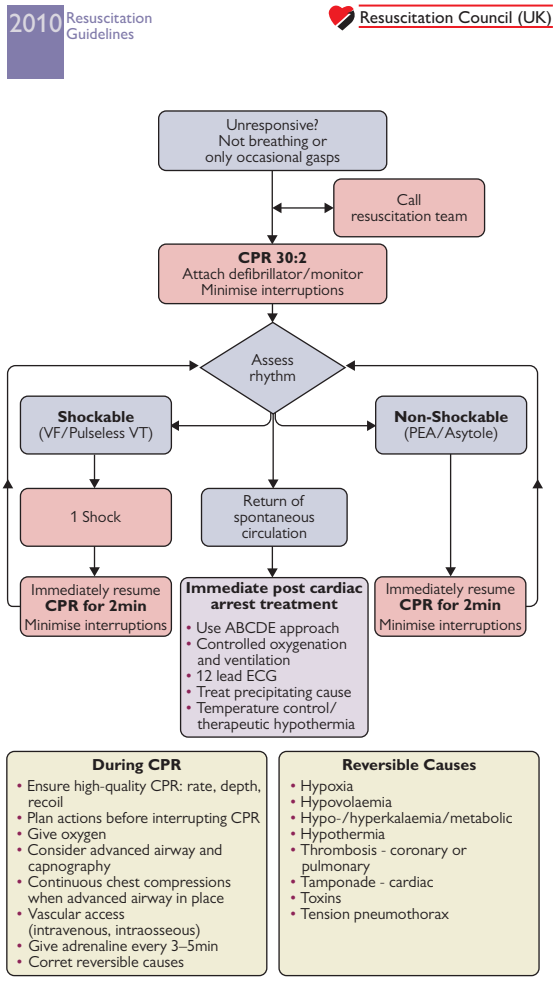


Fig. 1.2 Adult advanced life support algorithm.
Reproduced with the kind permission of the Resuscitation Council (UK).

- Lidocaine 100mg IV can be used as an alternative to amiodarone if contraindicated (not to be given concurrently).
- Magnesium sulphate (2g IV) if risk of hypomagnesaemia—patients on diuretic therapy.
- Check pad position and contacts. Consider change to anteroposterior position.
- If doubt over VF or asystole treat as non-shockable—continued shocks to possible fine VF is unlikely to prove successful with increased myocardial injury due to chest compression interruptions and direct electrical current.
- If patient's rhythm changes to PEA/asystole move to non-shockable rhythms.

Non-shockable rhythms: asystole/pulseless electrical activity (PEA)

- PEA is the absence of palpable pulsation in the presence of organized electrical activity.
- In the presence of asystole check carefully for present of p waves and ventricular standstill (option for pacing).
- Potential reversible causes should be identified and treated quickly, without which survival is unlikely.

Management

- As for basic life support.
- Establish IV access and consider intubation.
- Immediately give 1mg IV adrenaline.
- For PEA <60/minute: give 3mg IV atropine.
- Continue CPR at a rate of 30:2 (continuous cardiac compressions if intubated).
- Continue CPR for 2 minutes.
- Check monitor for rhythm.
- If organized electrical activity is seen, check for signs of life and pulse.
- If no pulse (PEA) or asystole: continue CPR for 2 minutes.
- Check monitor for rhythm.
- If organized electrical activity present check for signs of life and pulse.
- If no pulse or asystole: continue CPR for 2 minutes.
- 1mg IV adrenaline every alternate cycle.
- Intubation (tracheal) to protect the patient's airway and provide continuous cardiac compressions (during ventilation, cardiac perfusion pressure is severely reduced and takes time on resumption of compressions to be restored). Expert personnel only—each attempt should take no longer than 30 seconds.
- Assessment of tube placement is made by observing chest rise and auscultation in all areas.
- Ventilate at a rate of 10/minute.

Reversible causes

Survival from cardiac arrest is higher in the presence of a number of reversible causes, identified using the '4 Hs and 4 Ts' technique:

- **H**ypoxia—adequate ventilation with airway adjuncts and high-flow oxygen.
- **H**ypovolaemia—IV fluids to restore volume and stop haemorrhage—surgery etc.
- **H**yperkalaemia, hypokalaemia, hypoglycaemia—IV replacement (e.g. calcium chloride, IV glucose).
- **H**ypothermia—usually given from the history (e.g. drowning)—rapid re-warming to temp >30°C (drugs withheld until above this temperature).
- **T**ension pneumothorax—clinical diagnosis with urgent needle thoracocentesis (2nd intercostal space, midclavicular line).
- **T**amponade—consider in penetrating chest trauma, obtain emergency echo, needle pericardiocentesis or thoracotomy may be required.
- **T**hromboembolic—massive pulmonary embolism or myocardial infarct, consider thrombolytic therapy.
- **T**oxic—review of history may reveal toxic exposures. Antidotes for some drugs exist (naloxone, flumazenil) but should not be used speculatively.

Post-resuscitation care

Following return of spontaneous circulation, further intervention is required in order to stabilize cardiac function as much as possible.

Ongoing treatment of the airway, breathing, and circulation are important for maintaining haemodynamic stability and specialist care should be sought throughout this period.

Do not resuscitate decisions

Decisions should involve the patient and their families if possible. Of note, relatives do **not** have the power to make decisions on medical care on behalf of another person, but their opinion should be considered during any decision-making process.

These are difficult decisions and should take into account:

- Underlying condition makes successful outcome unlikely.
- Resuscitation is not in the patient's best interest in terms of poorer quality of life.
- A competent patient's stated or prior advance directive wish not for resuscitation.

1.2 Shock

Definition

Shock is the medical emergency of profound circulatory collapse resulting in reduced organ and tissue perfusion, requiring immediate intervention to prevent end-organ damage and ultimately cardiac arrest.

Types of shock

- Anaphylactic
- Cardiogenic
- Hypovolaemic
- Septic.

Examination

- Tachypnoea.
- Hypotension: systolic blood pressure (BP) <90mmHg.
- Tachycardia: heart rate (HR) >100/minute (care if taking β-blockers).
- Reduced capillary return: >2 seconds.
- Cool peripheries and cyanosis.
- Pallor.
- Confusion (cerebral hypoxia).
- Reduced urine output: <0.5mL/kg/hour.

Anaphylactic shock

Severe systemic allergic reaction with hypotension and/or respiratory problems.

Presentation

- Angio-oedema.
- Erythema.
- Urticaria.
- Pruritis.
- Swelling of upper airways (lips to epiglottis) and stridor.
- Shortness of breath and wheeze.

Management

- Immediate management = airway protection, administration of adrenaline (epinephrine), and fluid resuscitation.
- Discontinue causative agent if possible.
- Airway protection: severe laryngeal oedema may require intubation or surgical airway (needle cricothyroidotomy, tracheostomy).
- Oxygen delivery to maintain saturations >95%.
- IM adrenaline (epinephrine) 0.5mL of 1 in 1000.
- Repeat in 5 minutes if no clinical response.
- Continuous electrocardiograph (ECG) monitoring.
- Large-bore IV cannula (>18G/green).
- IV fluid resuscitation (colloid or crystalloid).
- IV antihistamine (e.g. chlorpheniramine 10mg).
- IV steroids (e.g. hydrocortisone 100mg).
- Salbutamol nebulizers (5mg) if wheeze present.
- Admit for 24 hours to observe for delayed reaction.
- Continue oral antihistamine for 24–72 hours.
- Supply preloaded adrenaline syringe to patients at risk of recurrence. Consider referral to local allergy/immunology service.

Cardiogenic shock

- Cardiogenic shock results from cardiac dysfunction impairing the ability to maintain adequate tissue perfusion.
- Mortality can range from 50–75% even with treatment.
- Defined clinically as reduced cardiac output and poor tissue perfusion in the presence of euvolaemia.

Presentation

- As for clinical definition, plus signs and symptoms of cause:
  - Myocardial infarction (MI).
  - Acute coronary syndrome (ACS).
  - Acute mitral regurgitation (MR; papillary muscle rupture).
  - Rupture of interventricular septum.
  - Myocardial suppressants, e.g. calcium antagonist overdose.
- Raised jugular venous pressure (JVP) and signs of pulmonary oedema.
- Pansystolic murmur of MR or ventricular septal defect (VSD).
- Evidence of endocarditis—splinter haemorrhages, etc.

Investigation

- Full blood count (FBC)—anaemia or raised white cell count (WCC; infection).
- Urea and electrolytes (U&Es)—renal dysfunction.
- Cardiac enzymes—troponin for MI.
- Lactate—evidence of poor tissue perfusion.
- Arterial blood gas (ABG) analysis.
- ECG—ischaemia, arrhythmia.
- Chest X-ray (CXR)—pulmonary oedema.
- Urgent echocardiography.

Management

- Aim: increase tissue perfusion to prevent end-organ damage and treat the cause.
- Early specialist cardiology input is imperative and these patients will require CCU/HDU/ITU support.
- Ensure patients have adequate fluid resuscitation (care with pulmonary oedema). Fluid resuscitation in right-sided myocardial infarctions may improve blood pressure, but **do not** overload as this may worsen symptoms.
- Continuous cardiac monitoring.
- Treatment of coronary ischaemia/infarction: antiplatelets, heparin, glycoprotein (GP)-IIb/IIIa inhibitors, thrombolysis, or primary percutaneous coronary intervention (PCI).
- Treatment of arrhythmia—DC cardioversion or pacing as indicated.
- Central venous access for fluid balance monitoring (and drugs) is often essential—beware of potential cardiac irritability (if myocardial ischaemia) during line insertion.

If persistent hypotension:

- Inotropic support (through central venous access) should be considered, aiming for a mean arterial pressure (MAP) of 60mmHg if possible:
  - Dopamine 5–10mcg/kg/min.
  - Noradrenaline 0.5mcg/kg/min (if dopamine fails to effect response).
  - Adrenaline.
- Placement of an intra-aortic balloon pump (to stabilize prior to definitive treatment, usually at a tertiary centre).
- Left ventricular assist device or urgent coronary artery bypass surgery may be required.

Hypovolaemic shock

Severe blood/fluid loss causing haemodynamic compromise.

Presentation

- Cause for hypovolaemic shock can often be identified by history—i.e. trauma, melaena, fresh bleeding, diarrhoea & vomiting.
- Degree of volume loss can often be estimated from the haemodynamic status of the patient (Table 1.1).

Investigation

- FBC and coagulation screen.
- U&Es—renal failure, raised urea with normal creatinine may indicate gastrointestinal (GI) haemorrhage.
- Group and save—haemorrhage should instigate a cross-match request for 4–6 units.
- ABG (or venous gas)—lactic acidosis indicates poor tissue perfusion.

Management

- Immediate management should involve fluid replacement, prevention of further fluid loss, and identification/treatment of the cause. Management should then focus on stabilization of the patient pending definitive management, i.e. surgery for ruptured abdominal aortic aneurysms (AAAs), embolization, endoscopy, etc.
- Airway protection if reduced Glasgow Coma Scale (GCS) score.
- Oxygen delivery—15L via non-rebreathe mask.
- Pressure on any open bleeding points.
- 2 × large-bore IV cannula (≥18G/green).
- IV fluid resuscitation—colloid/crystalloid, rapidly.
- Blood transfusion if haemoglobin (Hb) <10g/dL or massive haemorrhage (activate 'massive blood transfusion' protocol)
- Correction of coagulopathy if indicated: fresh frozen plasma (FFP), cryoprecipitate, Beriplex®, vitamin K.
- Consider central venous access for monitoring central venous pressure (CVP) to guide fluid replacement. Caution with central venous access (subclavian, jugular) if hypovolaemic, and remember ability to fluid resuscitate is limited through central access due to line gauge.

Urgent investigations

- Imaging:
  - Focused abdominal scan (ultrasound) for intra-abdominal bleeding ('rule in, not rule out', i.e. AAA).
  - Computed tomography (CT).
- Angiography: identify (and potentially embolize) source.
- Endoscopy (gastroscopy/colonoscopy): potential to inject/ligate bleeding point.

Table 1.1 Classification of hypovolaemic shock

Classification	1	2	3	4
Blood loss	<750mL	0.75–1.5L	1.5–2L	>2L
%	0–15	15–30	30–40	>40
Systolic BP	No change	No change	Reduced	Much reduced
Diastolic BP	No change	Increased	Reduced	Unrecordable
Pulse/minute	Increased	100–120	120	>120 + thready
Respiratory rate	Normal	Normal	Increased	Increased
Mental state	Normal	Anxious	Drowsy	Confused
	Thirsty		Aggressive	Unconscious

- Continued haemorrhage with persistent hypotension should precipitate **urgent** surgical referral.

Septic shock

- Sepsis = the presence of infection associated with a systemic inflammatory reaction.
- A set of clinical criteria, known as systemic inflammatory response syndrome (SIRS), provides a helpful indicator for the severity of sepsis:
  - Meeting two or more criteria should alert to the possibility of development of end-organ dysfunction and potential for septic shock.

Temperature:	<36°C	>38°C
Pulse:	>90/min	
Respiratory rate:	>20/min	pCO_2 <3.2
WCC:	>14	<4

- Septic shock = severe infection with associated hypotension despite adequate fluid resuscitation.

Presentation

- Pyrexia, flushed appearance.
- Rigors.
- Bounding pulse.
- Focal signs of localizing infection: i.e. meningism, cellulitis.
- Be aware: patients may present as flushed and warm, or cold and peripherally shut down.

Investigation

- FBC—raised WCC.
- U&Es—renal failure.
- Clotting—disseminated intravascular coagulation (DIC).
- C-reactive protein (CRP).
- Liver function test—possible biliary source?
- Blood cultures: prior to antibiotics if at all possible.
- Urinalysis and culture.
- Sputum/stool cultures, wound swabs (as indicated).
- ABG or venous gas (measure lactate).
- CXR—pneumonia, adult respiratory distress syndrome (ARDS).

Management

- Immediate management involves fluid resuscitation, administration of antibiotics, and removal of any septic foci.
- Administer oxygen to maintain saturations >95%.
- IV access and bloods.
- Administer broad-spectrum antibiotics as per local policy.
- Fluid resuscitation with colloid/crystalloid.
- Maintain Hb >10g/dL.
- Catheterization and hourly urine output monitoring.
- CVP monitoring—for fluid management and inotropes.
- Early specialist intensive care input.
- Continued hypotension after adequate fluid resuscitation (CVP 10–12mmHg) should necessitate inotropic use:
  - Noradrenaline 1–12mcg/min.
  - Adrenaline 1–12mcg/min.
  - Dobutamine 2.5–15mcg/kg/min.
  - Vasopressin.
- Further investigation as indicated to define infective source.

1.3 Acute coronary syndromes

Definitions

Acute coronary syndromes (ACS)

Symptoms consistent with myocardial ischaemia, including:

- ST-elevation myocardial infarction (STEMI).
- Non-ST elevation myocardial infarction (NSTEMI).
- Unstable angina.

Definition of MI (European Society of Cardiology)

- Elevated cardiac biomarkers (troponins).

With one or more of the following:

- New pathological Q waves.
- New or dynamic ST or T changes.
- New left bundle branch block (LBBB).
- Imaging of new myocardial dysfunction.
- Symptoms of ischaemia for >20 minutes.

In the patient presenting with symptoms suggestive of ACS (see also Section 3.3):

Initial assessment

- Airway, breathing, circulation.
- Ensure that airway is safe; commence high-flow oxygen therapy through a non-rebreathe mask.
- Check respiratory rate and oxygen saturations.
- Check HR and BP in both arms, attach continuous cardiac monitor, and obtain 12-lead ECG.
- Brief history—think about the differential diagnosis.
- Analgesia if required (e.g. diamorphine 2.5–10mg IV) + anti-emetic.

Differential diagnosis of chest pain

- Acute coronary syndrome
- Pericarditis
- Myocarditis
- Arrhythmias
- Pulmonary embolism
- Pneumonia
- Chest wall pathology
- Costochondritis (Tietze syndrome)
- Aortic dissection
- Gastro-oesophageal spasm or rupture
- Odynophagia
- Reflux disease
- Gallstones and biliary disease
- Herpes zoster

Investigations

ECG

ECG is fundamental to the diagnosis of ACS—a good quality tracing is required. Check the ambulance rhythm strip for paroxysmal arrhythmias which may be missed on a single ECG.

In a STEMI, look for:

- ST elevation of >2mm in more than two adjacent chest leads **or** >1mm in two adjacent limb leads.
- Concomitant ST depression in another area indicates reciprocal changes or multivessel disease.
- New LBBB (prolonged QRS duration, M pattern in V5–V6)—may need to check previous ECGs.
- Q waves may develop after several hours or days.
- T wave inversion develops over days to weeks.

Other conditions which may cause similar ECG changes include pericarditis, myocarditis, myocardial contusion, pulmonary embolism, hyperkalaemia, pancreatitis, and intracranial haemorrhage.

Cardiac enzymes

Troponins are the most sensitive and specific markers of myocardial ischaemia. Troponin levels begin to rise 3 hours after an event and may be elevated for 14 days. Troponin may also rise in pericarditis, pulmonary emboli, and arrhythmias.

Chest radiograph

Look for mediastinal widening and pulmonary oedema.

NSTEMI

- More common than STEMIs and tend to occur in older, comorbid, or hospitalized patients.
- Mortality at 6 months is similar to that of STEMI patients.
- Initial management is similar to that of STEMIs but there is no proven role for reperfusion therapy.

Initial assessment (see Fig. 1.3)

As listed earlier:

- Cardiac monitoring and regular ECGs to check for new changes.
- Measure troponin at 12 hours after onset of symptoms. Check potassium and magnesium and replace if low.

Anticoagulant and antiplatelet therapy

- Give aspirin 300mg and clopidogrel 300mg.
- Anticoagulate with low-molecular-weight heparin (LMWH; enoxaparin 1mg/kg 12-hourly), or unfractionated heparin (UFH) if risks of bleeding are high. Reduce dose if significant renal impairment.
- GPIIb/IIIa inhibitors such as abciximab, tirofiban, and eptifibatide are useful in patients with intermediate/high-risk features, concurrent diabetes, ST depression, or preceding angiography.
- Abciximab 0.25mg/kg IV bolus, then infuse 0.125mcg/kg/min (max. 10mcg/min) for 12–24 hours.
- Eptifibatide 180mcg/kg IV bolus (repeat bolus in 10min prior to PCI) then infuse 2mcg/kg/min for 3–4 days.
- Tirofiban 0.4mcg/kg/min IV over 30 minutes then infuse at 0.1mcg/kg/min for 2–4 days.

Other agents

- Nitrates—standard symptomatic therapy but no evidence of benefit in mortality. Give as glyceryl trinitrate (GTN) spray, buccal nitrate, or a GTN infusion (1 mg/hour: titrate to response).
- Beta-blockers—no proven role but give if no contraindication—e.g. metoprolol 50mg PO 8-hourly.
- Calcium channel blockers may be given with beta-blockers especially for ongoing pain. In the longer term, diltiazem may reduce event rate.
- Start high-intensity statin therapy.

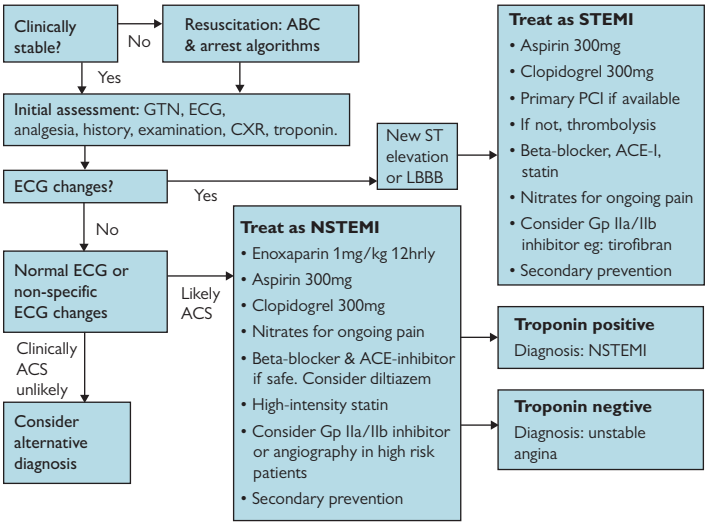


Fig. 1.3 Summary: management of patients presenting with ACS.

Invasive evaluation

- Consider angiography in patients with profound or dynamic ECG changes, life-threatening heart failure or arrhythmias, or with severe ongoing angina.
- Angiography within 72 hours of symptom onset followed by revascularization (PCI or coronary artery bypass graft (CABG)) is recommended.
- Many patients may be unsuitable due to comorbidities.

Afterwards

- Give lifestyle and driving advice (see under 'STEMI'). Refer for cardiac rehabilitation. Give anti-anginals if required.

STEMI

For patients presenting with symptoms and an ECG suggestive of STEMI:

- Initial management as for NSTEMI (see Fig. 1.3).
- Give oxygen, analgesia (+ anti-emetic), nitrates, and aspirin 300mg plus clopidogrel 300mg PO.
- Hypotensive patients should receive cautious 100–500mL boluses of fluid—if hypotension is prolonged, insert central access and consider inotropes.
- Auscultate for the murmur of acute MR.

Beta-blockers

- Early beta-blockade reduces mortality, infarct size, and complications.
- Especially useful if there is ongoing pain, hypertension, tachycardia, or tachyarrhythmias such as atrial fibrillation (AF).
- Avoid in: HR <60bpm, systolic blood pressure (SBP) <100mmHg, atrioventricular (AV) block, moderate to severe heart failure (negatively inotropic), peripheral vascular disease with ischaemic limb. Caution in inferior infarcts affecting the right ventricle.
- Start with metoprolol 2.5–5mg IV every 1–2 minutes (max. 15–20mg) to achieve a SBP of ~100–110mmHg with a HR of 60–100bpm. If this is tolerated well, start 50mg PO 8-hourly.

Angiotensin-converting enzyme (ACE) inhibitors

- ACE inhibitors also offer a mortality benefit—high-risk patients, the elderly, and those with large infarcts or concomitant heart failure benefit most.

Box 1.1 Reperfusion therapy in STEMI

Primary PCI

- Gold standard: reduces mortality, reduces further events, and confers better long-term left ventricular function and improved anginal symptoms compared to patients treated with thrombolysis.
- Indications: all patients with chest pain and ECG changes suggestive of STEMI are potentially suitable.
- Complications occur in ~1%: stroke, significant bleeding at puncture site, recurrent infarct, emergency CABG, death.
- Consider discharge in 72 hours.

Thrombolysis

- Indications: symptoms suggestive of myocardial ischaemia for <12 hours with typical ECG changes.
- Absolute contraindications: active internal bleeding, suspected aortic aneurysm, brain tumour, haemorrhagic stroke (ever), ischaemic stroke (within 1 year), recent head trauma, surgery within 2 weeks with bleeding risk.
- Relative contraindications: surgery >2 weeks previously, severe hypertension (SBP >180mmHg), warfarin use with INR >2, prolonged CPR (>10 minutes), previous ischaemic stroke >1 year previously, menstruation, liver or renal impairment.
- Complications (10%): bleeding, intracranial haemorrhage, allergic reactions to older agents, arrhythmias, embolization of plaque.
- Doses:
  - Alteplase: 15mg IV bolus then 0.75mg/kg for 30 minutes, then 0.5mg/kg for 60 minutes. Max. 35mg.
  - Reteplase: 10mg IV bolus. Repeat after 10 minutes.
  - Tenecteplase: give a bolus of 0.5mg/kg over 10 seconds. Max. 50mg.
  - Anistreplase: give a bolus of 30mg over 2–5 minutes IV.
- Consider discharge in 5–7 days.

- Start ramipril 1.25mg PO. The dose can be up-titrated over several days if tolerated. Monitor renal function.

Reperfusion therapy

- Reperfusion treatment must be carried out as soon as possible after symptom onset—ideally within 4 hours, when 50–70% patients are successfully reperfused with thrombolysis, and 70–90% with primary PCI (Box 1.1).
- Primary PCI is the treatment of choice but is not available in all areas.

Afterwards

- Consider enoxaparin 1mg/kg 12-hourly, especially post-thrombolysis.
- Consider GPIIb/IIIa inhibitors post-PCI—check local protocol.
- Continue daily aspirin 75mg, clopidogrel 75mg, ACE inhibitor, and beta-blocker.
- Risk stratification with submaximal exercise test, stress echo, or angiography particularly in high-risk patients with further chest pain, arrhythmias, or poor LV function.
- Start a high-dose statin (atorvastatin 80mg).
- Discuss lifestyle factors, exercise, smoking cessation, and dietary advice.
- Avoid driving for 1 week after successful PCI, 4 weeks after MI with no/unsuccessful PCI, or for 6 weeks for group 2 licence holders.

1.4 Tachycardia

Definition

Tachycardia is a fast heart rate, >100 beats per minute (bpm) (see Section 3.4). This may be symptomatic or asymptomatic. Not all tachycardias are pathological: sinus tachycardia can be normal.

History

- Ask about associated chest pain, syncope/pre-syncope, or breathlessness.
- Ask about caffeine, alcohol, and illicit drug use.
- Check for family history of arrhythmias and sudden death.

Examination

- Auscultate for murmurs, added heart sounds, and pulmonary oedema.
- Listen for a carotid bruit.
- Look for features of systemic disease: exophthalmos in Graves disease, malar flush, chronic liver disease.

Investigations (in the acute setting)

- ECG.
- Investigation should include potassium, magnesium, and thyroid function. Check Hb (anaemia).
- In acute symptomatic disease, consider CXR and ABG.

Sinus tachycardia

Heart rate can be increased in exercise, fever, anaemia, pregnancy, thyrotoxicosis, and acute pulmonary embolism.

Identify the cause and treat if required.

Narrow complex tachycardia

These arrhythmias arise from the atria or nodal areas and include atrial fibrillation/flutter, supraventricular tachycardia (SVT), and junctional rhythms. The QRS duration is <120ms.

Atrial fibrillation/flutter

- Some or all beats can be conducted giving 1:1 to 3:1 AV blocks. On other occasions the block can be variable.
- In fibrillation, beats are erratic and the ECG may show absent or variably sized p waves (Fig. 1.4).
- In flutter, there are regular 'saw-tooth' waves (Fig. 1.5).
- AF may present as acute, paroxysmal, or chronic disease.

Treatment of atrial fibrillation/flutter

Acute management

- Resuscitation—'ABC', IV access, monitoring.

Stable (SBP >90mmHg)

- If BP is adequate, give a beta-blocker—slows rate and helps reversion to sinus rhythm, e.g. metoprolol 50mg, two to three times daily. Caution in patients with pulmonary oedema.
- An alternative is amiodarone, given through a large-bore venous access, ideally a central line: 5mg/kg (usually around 300mg) IV over 1 hour, then 900mg over 24 hours.
- In young patients, or those without ischaemic heart disease, flecainide (2mg/kg IV over 25 minutes or 300mg orally) may be helpful. In patients who respond, it can be used as a 'pill in the pocket' regimen for paroxysmal AF. Flecainide is not advised in atrial flutter as it can provoke a 1:1 block and worsening tachycardia.
- If BP poor (SBP 90–110mmHg), consider digoxin (a weak inotrope). Dose according to weight—give two loading doses of 250–500mcg PO/IV 6 hours apart, then start daily dosing at 125–250mcg. Check levels after several days. Reduce maintenance doses with renal impairment.

Unstable (SBP <90mmHg)

- DC cardioversion may be appropriate if decompensated.
- Ask for anaesthetic help: patients need sedation or a brief general anaesthetic. Cardiovert with 120–150J biphasic (synchronized); deliver two further shocks at higher energy levels if initially unsuccessful.
- Use lower energy levels (e.g. start at 70–120J biphasic) in atrial flutter.
- IV amiodarone if unsuccessful.

Supraventricular tachycardia (SVT)

This arrhythmia is commonly paroxysmal and occurs at ~140–250bpm.

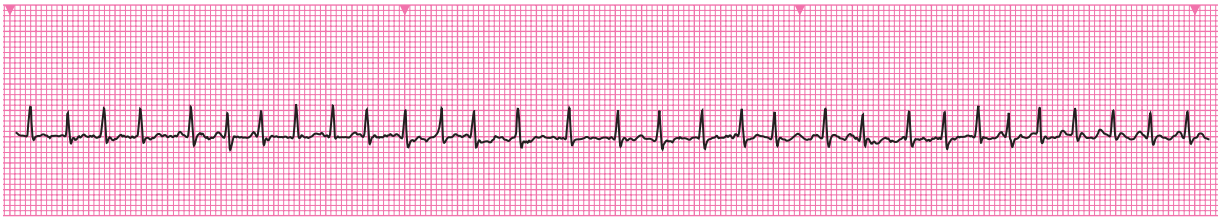


Fig. 1.4 Fast atrial fibrillation with a ventricular response of 236bpm. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

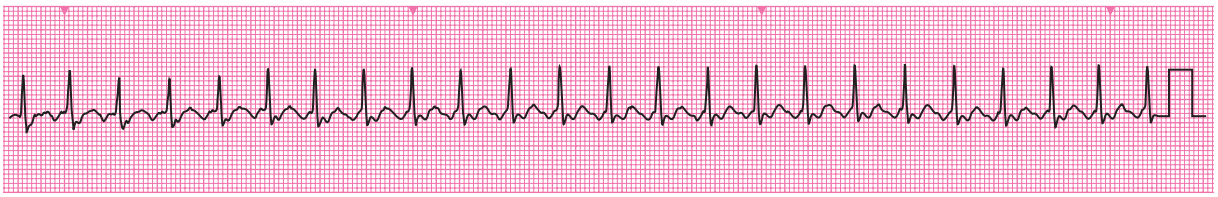


Fig. 1.5 Atrial flutter with sawtooth pattern and 2:1 block. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

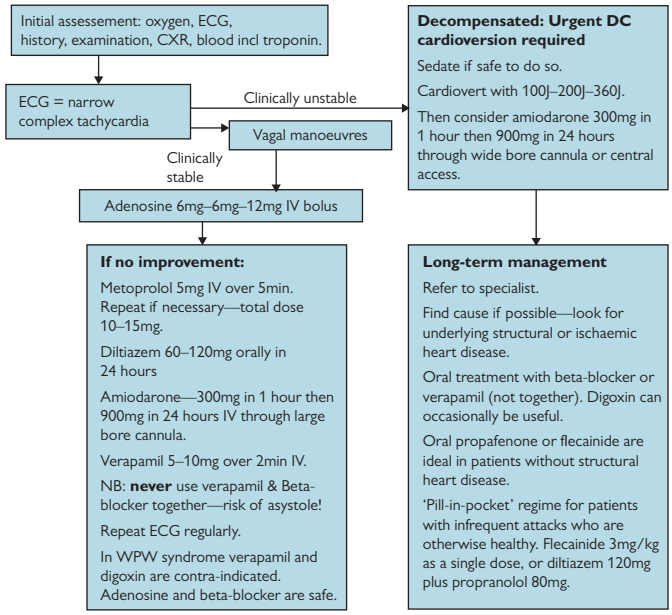


Fig. 1.6 Summary: management of patients presenting with supraventricular tachycardia (SVT).

Treatment

- Vagal manoeuvres (e.g. Valsalva manoeuvre, carotid sinus massage) may occasionally restore sinus rhythm (Fig. 1.6).
- Adenosine: initially, give 6mg quickly through a large-bore cannula: elevate arm, and immediately flush with 10mL saline. This will cardiovert some patients, and allows identification of underlying rhythm in others. If unsuccessful, give up to three further bolus doses in 3mg increments (up to 12mg). Patients experience a sense of impending doom due to transient AV block: warn them!
- If this does not work, consider beta-blockers, verapamil, diltiazem, or amiodarone.
- Avoid beta-blockers and adenosine in patients with significant asthma, and IV verapamil in patients already taking beta-blockers.
- As with patients in AF, if the patient is unstable or deteriorating, consider urgent DC cardioversion.

Wolff–Parkinson–White (WPW) syndrome

- When treating patients with WPW syndrome, avoid digoxin and verapamil. Beta-blockers and adenosine are safe.

Broad complex tachycardia

These arrhythmias have QRS >120ms and usually arise from the ventricles.

Ventricular tachycardia (VT)

- Patients with VT (Fig. 1.7) may present with a spectrum of clinical effects, from palpitations and breathlessness to cardiac arrest. Some patients attend outpatient clinics with a history of episodic collapse.
- Treatment—see Fig. 1.8.
- Those in peri-arrest situations with hypotension, cardiac failure, and severe symptoms should be assessed for urgent DC cardioversion. Conscious patients should be sedated prior to cardioversion if it is safe to do so.
- A minority of patients presenting with VT are relatively stable. These patients could be treated with amiodarone intravenously.
- Untreated, VT can result in VF and cardiac arrest. All patients should receive continuous cardiac monitoring usually in a coronary care unit setting.
- Consider the cause: check troponin in case of myocardial infarction, check electrolytes and replace if necessary. If the cause is not clear, refer for investigation.

Torsades de pointes

- Torsades de pointes is a variation of VT causing a regular broad complex pattern on ECG which waxes and wanes as the axis changes (Fig. 1.9).
- Torsades de pointes can occur when there is prolonged ventricular repolarization, with a long QT interval on ECG (Box 1.2).
- Treat (see Fig. 1.8) and address the underlying cause.

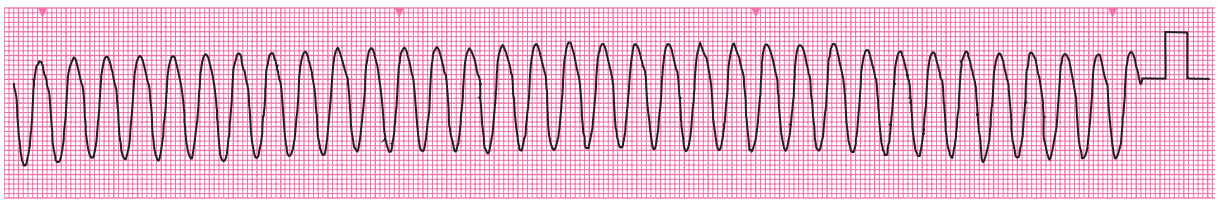


Fig. 1.7 Ventricular tachycardia (VT): regular broad complex tachycardia. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

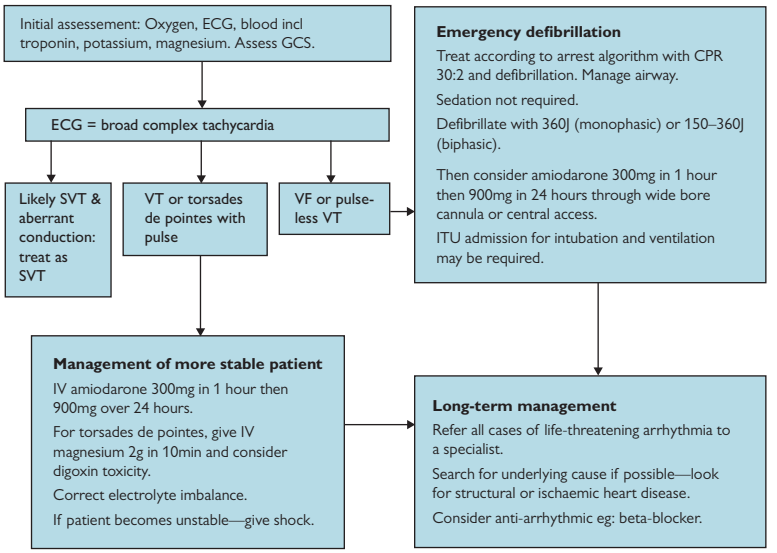


Fig. 1.8 Management of broad complex tachycardia.

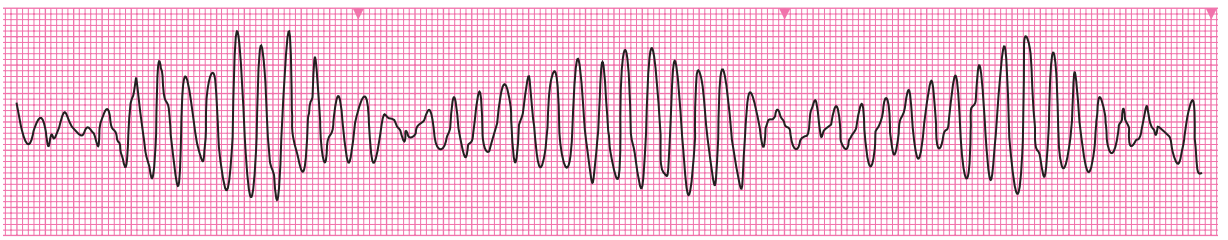


Fig. 1.9 Torsades de pointes: regular rotating broad complex tachycardia. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

Box 1.2 Causes of prolonged QT interval and torsades de pointes

Congenital:
- Romano–Ward syndrome
- Jervell and Lange–Nielson syndrome.

Drugs:
- Class Ia anti-arrhythmics, e.g. quinidine, procainamide
- Class III anti-arrhythmics, e.g. amiodarone, sotalol
- Tricyclic antidepressants, e.g. amitriptyline
- Macrolides, e.g. erythromycin

Electrolyte disturbance:
- Hypokalaemia
- Hypomagnesaemia
- Hypocalcaemia

Pathological/physiological:
- Prolonged fasting
- Mitral valve prolapse
- Acute myocardial infarction
- CNS disease

Ventricular fibrillation (VF)

VF is not compatible with life: patients present with cardiac arrest. There may be occasional fibrillation pulse beats felt, but there is an absence of a regular, functional pulse.

- In VF, the ECG shows irregularly sized broad complexes of chaotic ventricular activity (Fig. 1.10).
- VF should be treated according to the cardiac arrest algorithms with prompt defibrillation and CPR.
- A common cause of VF is myocardial infarction. With prompt successful defibrillation, the prognosis for these patients is reasonably good.

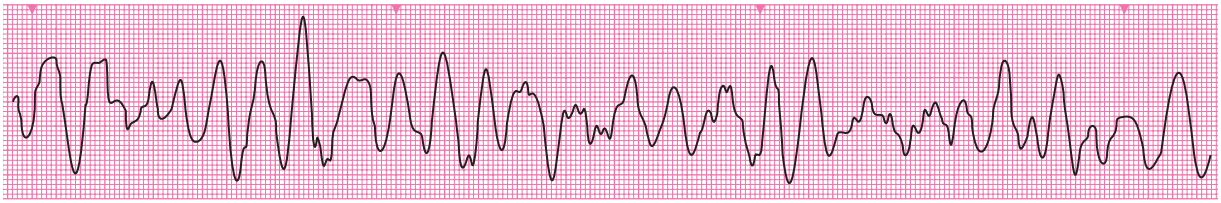


Fig. 1.10 Ventricular fibrillation (VF): irregular broad complex tachycardia. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

1.5 Bradycardia

Definition

- Bradycardia is a slow HR, <60bpm.
- For some patients, this represents normal variation between individuals.
- At night, the HR can drop to 50bpm.
- Consider treating patients with HR <40bpm or with symptoms of bradycardia (see Section 3.4).

History and examination

- Ask about palpitations, dizziness, collapse, chest pain, ankle oedema, breathlessness, and family history of sudden death.
- Ask about medication—any changes recently?
- Look for signs of cardiac failure, cardiomegaly, or previous cardiac surgery.
- Auscultate for murmurs.
- Look for features of hypothyroidism or connective tissue diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Investigations

- Observations including BP, HR, and temperature are fundamental to the initial assessment.
- ECG and rhythm strip—repeat regularly.
- Blood tests including FBC, U&Es (especially K^+), calcium, magnesium, thyroid function, and possibly troponin.
- CXR—to check for pulmonary oedema and cardiac size.
- Haemodynamically unstable patients should receive continuous cardiac monitoring.

Sinus bradycardia

There is a P wave prior to every QRS complex but rate <60bpm.
Causes include:

- Normal variation.
- Medications such as beta-blockers and digoxin.
- Sick sinus syndrome.
- Hypothyroidism.
- Hypothermia.

This rhythm does not always need treatment, particularly if the patient is asymptomatic. If medication is the cause, consider reducing the dose or changing to an alternative agent.

Heart block

First-degree heart block

Long PR interval (>0.2 seconds), can be normal variation (Fig. 1.11).

Second-degree heart block

Mobitz I (Wenkebach)—PR interval increases over several beats with eventual absent QRS (Fig. 1.12).
Mobitz II—unconducted P waves which can have a regular pattern (e.g. 3:1 or 2:1). PR interval remains constant (Fig. 1.13).

Third-degree (complete) heart block

Complete dissociation of atrial and ventricular beats. P waves are not followed by QRS complexes (Fig. 1.14).

Treatment of bradycardias

Treat all patients with symptoms or HR <40bpm.

- Medications such as beta-blockers and digoxin should be stopped or doses reduced.
- Oxygen if hypoxic or unstable.
- Atropine 0.6–1.2mg IV repeated to maximum dose of 3mg.
- Isoprenaline 0.2mg IV. If patient remains unstable, start an infusion at 1mg in 100mL saline and infuse at 1mcg/min. Titrate up according to HR response.
- Secure good venous access in all patients—many may require central access.
- In stable but symptomatic patients, admit and consider pacemaker insertion.
- In severely compromised patients (cardiac arrest, asystole, hypotensive (SBP <90mmHg), confused, or hypoxic due to pulmonary oedema), consider pacing to maintain output.
- Consider external pacing in an emergency setting or post-infarct/thrombolysis. External pacing is uncomfortable and should be used as a temporary measure only until a pacing wire can be inserted. Patients may require sedation to tolerate external pacing.
- A transvenous pacing wire is a more comfortable option for patients but is a more challenging procedure. Central access is

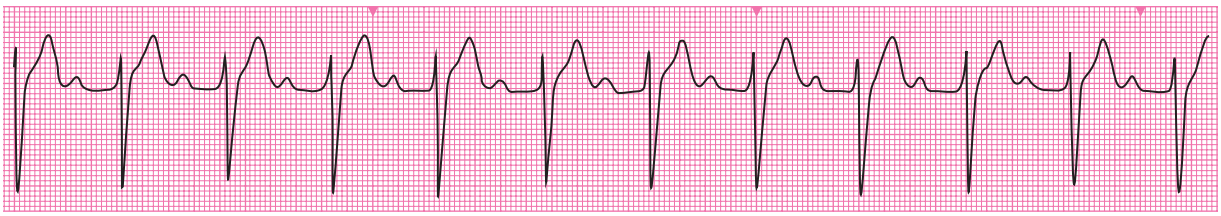


Fig. 1.11 First-degree heart block. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

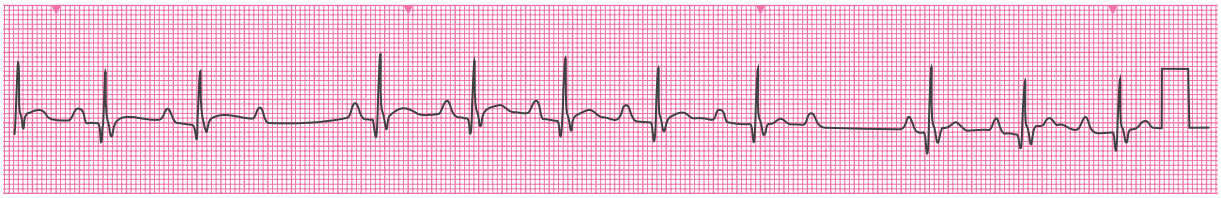


Fig. 1.12 Mobitz type I (Wenckebach) second-degree heart block. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

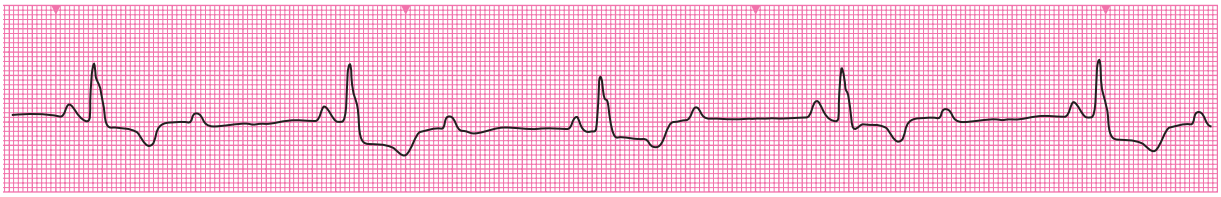


Fig. 1.13 Mobitz type II second-degree heart block. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

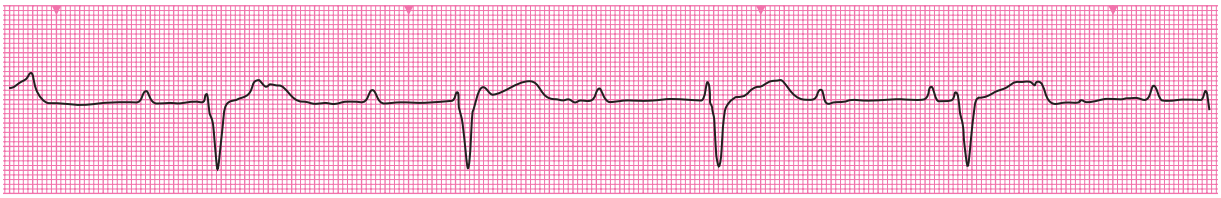


Fig. 1.14 Third-degree (complete) heart block. Reproduced with the kind permission of Dr. med. Oliver Meyer, MME.

obtained, usually via the left internal jugular vein, and a pacing wire is fed carefully into the right atrium and through the tricuspid valve. The pacing wire is then manoeuvred to place the tip of the wire at the tip of the right ventricle. Position and pacing effect are checked. Once the wire is in a satisfactory position, pacing can commence at around 70bpm. Check the rhythm strip to ensure there is successful capture. Risks of the procedure include perforation, pneumothorax, tamponade, diaphragmatic pacing, and arrhythmias.

Permanent pacemakers

- The definitive treatment for persistent or symptomatic bradycardias.
- Consider a pacemaker for patients with:
  - Complete AV block
  - Mobitz type II block
  - Persistent AV block post-infarct
  - Sick sinus syndrome
  - Symptomatic bradycardias
- The pacemaker is usually inserted just under the skin around the left pectoral area. The procedure is straightforward and done under local anaesthetic with few major complications. Prophylactic antibiotics may be given.
- Suspect pacemaker malfunction if there is bradycardia with no pacing spikes, if there are spikes with no capture, or if there are inappropriate spikes.
- Pacemakers can last up to 15 years and require an annual pacing check.

1.6 Hypertensive emergencies

Definitions

- A hypertensive **crisis** constitutes an acute, severe elevation in arterial blood pressure (typically SBP >200mmHg, DBP >130mmHg) with significant threat of microvascular damage, if the rate of change is rapid.
- A hypertensive **emergency** implies the presence of end-organ damage, which will become irreversible within a matter of hours if sustained. Examples include encephalopathy, retinal haemorrhages, papilloedema, and acute kidney injury (AKI).
- A hypertensive **urgency** may have 'softer' symptoms, without demonstrable end-organ damage, but threatens the same within days if left untreated.
- Classifications are ultimately somewhat academic and a general approach to evaluation and management is presented here. If in any doubt seek senior/specialist support early. In specialist centres, clinical pharmacologists offer expert advice.

Presentation

- May be asymptomatic.
- Non-specific symptoms, e.g. mild headache, epistaxis.
- Features of renal damage (hypertensive nephrosclerosis):
  - Haematuria
  - Proteinuria
  - AKI
- Neurological complications/encephalopathy:
  - Severe headache
  - Nausea and vomiting
  - Focal neurological deficits
  - Fits
  - Confusion
  - Coma
  - Intracranial haemorrhage
- Visual symptoms/signs:
  - Retinopathy/papilloedema
- Cardiovascular symptoms/associations:
  - Chest pain
  - Myocardial infarction
  - Left ventricular failure with pulmonary oedema
  - Aortic dissection
- Features of precipitating condition:
  - Phaeochromocytoma
  - Pregnancy (eclampsia/pre-eclampsia)
  - Chronic renal disease
  - Rheumatological conditions
- In the context of acute withdrawal of antihypertensive therapy.

Ask about/look for previous history of hypertension to help determine the rate of elevation.

Examination

- Fundi (looking in particular for grade 3 or 4 retinopathy with progression to bilateral retinal haemorrhages, exudates, and papilloedema).
- BP in both arms.
- Cardiomegaly.
- Left ventricular function.
- Peripheral pulses.
- Renal masses.
- Focal neurology.

Investigations

- FBC: microangiopathic haemolytic anaemia (MAHA).
- U&Es: renal failure/hypokalaemia.
- Clotting: disseminated intravascular coagulation (DIC).
- CXR: cardiomegaly, pulmonary oedema, widened mediastinum.
- Urinalysis: blood/protein/casts.
- Glucose: always important to check if encephalopathy.

Consider:

- Urine albumin:creatinine ratio (ACR).
- Urinary/plasma metanephrines.
- Plasma renin/aldosterone.
- Echo: left ventricular hypertrophy (LVH)/dissection.
- Renal ultrasound scan (USS): renal size.
- Magnetic resonance (MR) renal angiogram: renal artery stenosis.
- CT aortography: aortic dissection.
- CT head: intracranial haemorrhage.
- Toxicology screen: cocaine, amphetamines.

Admission criteria

- DBP persistently >120mmHg.
- Retinal haemorrhages or papilloedema.
- Encephalopathy or focal neurology.
- AKI.
- Suspicion of dissection, phaeochromocytoma, pre-eclampsia, eclampsia, or cardiac disease.

Management principles

In general, the cardinal rule is that rapid reduction of BP is dangerous and should be avoided. Cerebral blood flow autoregulation is disturbed in severe hypertension and local flow can drop precipitously leading to watershed infarcts. Cortical blindness, myocardial infarction, and death may also ensue.

The main focus of treatment is thus to lower BP in a controlled manner. Normality is **not** the desired endpoint. This is more important than the choice of agent. Longer-acting antihypertensives are favoured and oral medications have a better side effect profile. Short-acting oral and sublingual agents should be avoided. Beta-blockers and long-acting calcium channel blockers are reasonable first-line treatments with a reduction target of ~20mmHg BP per day.

More rapid reversal of extreme hypertension is, however, mandated in aortic dissection and myocardial infarction.

A comprehensive discussion of available antihypertensive agents and their properties is beyond the scope of this chapter. Local guidelines may exist or consult the BNF.

Acute management of the hypertensive emergency

- Transfer the patient to a high dependency setting.
- Consider arterial and central venous monitoring.
- Catheterize and monitor urine output.
- If early features: use oral therapy (e.g. amlodipine 5mg).

- Parenteral treatment is indicated with late symptoms or deterioration. Titratable medications given as continuous infusions are preferred. Suggested first-line approaches in specific presentations are discussed as follows.

Hypertensive emergency with retinopathy

- Beta-blockade (e.g. labetalol bolus followed by infusion, aiming for reduction to 100mmHg DBP or 20–25mmHg/day, whichever is the lesser reduction).

Hypertensive emergency with encephalopathy

- Sodium nitroprusside/GTN as first line, aiming for 25% reduction in diastolic BP over 1–2 hours.

Hypertensive emergency in context of stroke/intracranial haemorrhage

- Only treat, and then with caution, if DBP >130mmHg *and* clinical signs of cerebral oedema. Neurology/neurosurgery input advised.

Hypertensive emergency with acute LVF

- Opiates, furosemide, and sodium nitroprusside/GTN.

Hypertensive emergency with AKI

- Treat AKI as per Sections 1.11 and 17.6.
- Nephrology input advised.

Hypertensive emergency in context of phaeochromocytoma

- Alpha-blockade with phentolamine and/or phenoxybenzamine.

Hypertensive emergency in context of aortic dissection

- Beta-blockade (e.g. labetalol), sodium nitroprusside/GTN.
- Aim to reduce SBP to 100–120mmHg rapidly. Cardiology/cardiothoracic input advised.

Hypertensive emergency in eclampsia/pre-eclampsia

- Deliver the baby.
- Magnesium sulphate/hydralazine.

Summary

Management should usually be in a high-dependency setting with early specialist input. After the acute phase, BP should be gradually and cautiously normalized under the care of a specialist cardiology or clinical pharmacology team.

1.7 Pulmonary oedema

Definition

- The extravasation of fluid from the pulmonary circulation into the interstitial spaces and alveoli of the lung.
- Causes acute or chronic breathlessness and may be accompanied by wheeze and expectoration of pink, frothy sputum.

Aetiology and diagnosis

Pulmonary oedema has many causes, although it is most commonly due to cardiac disease. Causes include:

- Cardiac failure with inadequate left ventricular function.
- Obstructed flow through the left heart: tamponade, cardiomyopathy, myxoma, or valvular disease.
- High output states: anaemia, thyrotoxicosis, or shunts.
- Renal causes: acute or chronic renal failure or renal artery stenosis with hypertension.
- Hypoalbuminaemia of any cause such as liver failure, nephrotic syndrome, or a systemic inflammatory response.
- Infection, including aspiration.
- ARDS.
- DIC.
- Lymphangitis carcinomatosis: blockage of lymphatic ducts.
- Other causes: including prescribed medication (e.g. NSAIDs, beta-blockers), eclampsia, alcohol, altitude, heroin, and drug overdoses.

Immediate management for acute cardiac failure

- Give oxygen to maintain saturations >95% (>90% in chronic obstructive pulmonary disease (COPD) patients). Monitor with ABGs.
- IV access, continuous ECG monitoring and regular measurement of BP.
- Diuretic treatment should be initiated promptly. Give 40–100mg furosemide IV and reassess. Many patients require repeated doses.
- Give IV diamorphine 2.5–5mg IV (and IV anti-emetic).
- If SBP >90mmHg give sublingual GTN (two puffs) or buccally (2mg or 5mg buccal tablet).
- Reassess patient—is pulmonary oedema the correct diagnosis and is the underlying cause apparent?—see Box 1.3. Send blood samples and arrange urgent CXR.
- If SBP>100 mmHg commence nitrate infusion (caution may be required to maintain BP): start with 0.5–10mL/hour (start at 1mL/hour) of 50mg GTN in 50mL of saline and titrate carefully to achieve symptom control while maintaining SBP >90mmHg.
- Consider further doses of diuretic if not improving.
- Non-invasive ventilation such as continuous positive airway pressure (CPAP) improves left ventricular function by reducing afterload. Start with a positive end-expiratory pressure of 5cmH_2O and titrate up to 10cmH_2O with a FiO_2 of >40%.
- Consider referral to ITU and invasive ventilation in patients with insufficient oxygenation despite high-flow oxygen administration. Early referral improves survival.
- If SBP <100mmHg then consider inotropic support and ITU/HDU level care, especially if hypotension, cardiogenic shock, and evidence of tissue hypoperfusion, such as acidosis, clammy

Box 1.3 Clinical features of pulmonary oedema

- Breathlessness, exertional or constant.
- Cough, productive of pink, frothy sputum in severe disease.
- Basal coarse crepitations.
- Cyanosis.
- Fluid overload with pleural effusions.

Look for the underlying cause—clinically

- Take a careful history, particularly of medication use.
- Orthopnoea and paroxysmal nocturnal dyspnoea are typically cardiac symptoms.
- S3 gallop rhythm indicates left ventricular failure or fluid overload states.
- Listen for features of valvular disease.
- Look for signs of right heart failure (pulsatile hepatomegaly, raised JVP, peripheral oedema) which would indicate congestive cardiac failure.
- Conjunctival pallor in anaemia.
- Goitre, tremor, lid lag, or proptosis in thyrotoxicosis.
- Signs of alcohol use: parotid swelling, spider naevi, and other stigmata of chronic liver disease.
- Petechial rash with bruising or ecchymosis in DIC.

Look for the underlying cause—investigations

- Do an ECG to check for arrhythmias or MI.
- CXR is essential to confirm a clinical diagnosis.
- FBC, clotting, U&Es, LFT, TFT.
- Check troponin to identify ACS.
- CT may be indicated where the diagnosis is unclear, and is useful for lymphangitis carcinomatosis.
- Consider echocardiography.

CXR evidence of pulmonary oedema

- Blunting of costophrenic angle or frank pleural effusions, usually bilateral (see Fig. 1.15).
- Fluid in the horizontal fissure (Fig. 1.15: right mid-zone).
- Kerley B lines (horizontal lines).
- Upper lobe diversion.
- Fluffy-looking infiltrates throughout lung fields in severe disease.
- Think about cause: look for cardiomegaly, valve replacements, and sternotomy wires.

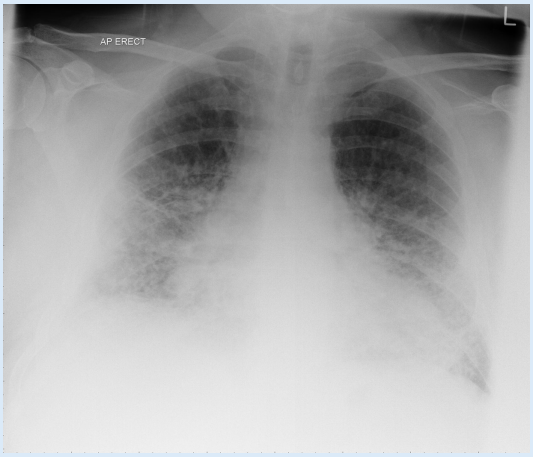


Fig. 1.15 Antero-posterior chest radiograph of patient with pulmonary oedema showing bilateral fluffy infiltrates, fluid in the horizontal fissure, and upper lobe blood vessel diversion.

peripheries, or confusion. Consider dobutamine (2–3mcg/kg/min) or dopamine (2–3mg/kg/min) with continuous cardiac monitoring.

Also:

- Catheterize patients to measure fluid output.
- Renal function must be carefully monitored as most treatments have a nephrotoxic effect.
- Haemodialysis or haemofiltration may be required for patients with concomitant cardiac and renal failure.
- *In extremis*, venesection (e.g. 500mL) is an option but rarely undertaken in practice.
- Address the underlying cause: e.g. patients with a new ischaemic event may require treatment for acute coronary syndrome.

1.8 Acute asthma

Background

Acute, severe asthma is a medical emergency and a common cause of morbidity and mortality in children and young adults (see Section 18.12).

Classification according to British Thoracic Society guidelines

Moderate exacerbation of asthma

- Peak expiratory flow rate (PEFR) 50–75% best or predicted.
- Increasing symptoms.
- No features of acute severe asthma.

Acute severe asthma

One of the following:

- PEFR 33–50% best or predicted.
- Respiratory rate >25/minute.
- Heart rate >110/minute.
- Unable to complete sentences in one breath.

Life-threatening asthma

One of the following:

- PEFR <33% best or predicted.
- Oxygen saturation <92%.
- PaO_2 <8kPa.
- Silent chest.
- Cyanosis.
- Poor respiratory effort.
- Arrhythmia.
- Exhaustion or reduced conscious level.

Near-fatal asthma

One of the following:

- Rising $PaCO_2$ levels.
- Requiring mechanical ventilation.

Investigations

- CXR if there is suspected infection, pneumothorax, or features of life-threatening asthma. Do **NOT** send the patient to the radiology department.
- Pulse oximetry—concerns develop if saturations <92%.
- ABGs—show type 1 respiratory failure initially. A low $PaCO_2$ suggests that the patient is not yet tiring. A rising $PaCO_2$, even into the reference range, should prompt consideration of treatment escalation.

Management

- Involve senior colleagues early (including anaesthetists).
- Oxygen therapy (at least 60% with a high-flow mask) to maintain saturations >94%.
- Inhaled or nebulized β_2 agonist bronchodilator, e.g. salbutamol 2.5–5mg nebs 4–6-hourly and additionally as required (up to every 15 minutes).
- Nebulized ipratropium bromide (0.5mg 4–6-hourly) in patients with acute severe or life-threatening asthma or in those with inadequate response to previous therapies.
- Nebulizers should be oxygen-driven.
- Steroids are essential—give IV hydrocortisone 100–200mg initially or oral prednisolone (30–50mg) if able to swallow. Continue either 100mg IV four times a day or prednisolone 30–50mg for at least 5 days. Oral steroids are preferred after the initial presentation as they have a longer duration of action than intravenous alternatives.
- Magnesium sulphate 1.2–2g infused IV over 20 minutes is used in patients who are not improving after initial measures (single dose only).
- Consider an IV salbutamol and/or aminophylline infusion in those with severe asthma or when there is clinical deterioration in spite of other treatments.
- Do not give a loading dose of aminophylline in those taking oral theophyllines and check levels daily. Reduce the dose in those with cirrhosis or congestive heart failure and in those taking erythromycin or ciprofloxacin.
- Patients should not be given antibiotics routinely unless there is convincing evidence of infection, e.g. fever, raised CRP, raised WCC, or consolidation on CXR.
- Repeated and regular clinical assessment is warranted including ABGs and PEFR measurements.
- Ensure that the patient is properly hydrated. Remember that β_2 agonists may lower serum potassium levels.
- In the longer term, patients with severe or life-threatening asthma should receive respiratory outpatient follow-up.
- Check inhaler technique in patients with frequent exacerbations.

Which patients may be suitable to send home?

- Patients with no features of life-threatening asthma or no features of acute severe asthma following initial treatment.
- Patients with PEFR ≥75% predicted 1 hour after treatment.

Which patients require referral to ITU?

- Those with severe and life-threatening asthma, failing to respond to therapy.
- Hypoxia, PaO_2 <8kPa despite 60% inhaled O_2.
- Hypercapnia, rising or $PaCO_2$ > 6kPa.
- Exhaustion, deteriorating conscious level, or coma.

Differential diagnosis—is it really asthma?

Other diagnoses to consider:

- Pulmonary embolism—may present with wheeze.
- COPD—ask about smoking history and look for type 2 respiratory failure.
- Foreign body—can cause wheeze and stridor particularly common in children.
- Cystic fibrosis—often presents in childhood with persistent cough, wheeze and recurrent infections.
- Eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome)—systemic vasculitis causing eosinophilic asthma, pulmonary haemorrhage with haemoptysis, and renal impairment.
- Tracheomalacia—softening of the tracheal cartilage causes airways obstruction, wheeze, and stridor.
- Alpha-1 antitrypsin deficiency—often misdiagnosed as asthma in early stages. Check liver function.
- Gastro-oesophageal reflux disease—recurrent minor aspiration of acid may cause chronic cough, wheeze, and mild breathlessness. Consider a trial of a proton pump inhibitor.

1.9 Massive pulmonary embolism

Background

Pulmonary embolism (PE) is diagnosed in around 1 in 1000 patients per year and is an important unrecognized cause of death with a prevalence of 1–8% in postmortem studies (see Section 18.14).

Clinical features of massive PE

- Pleuritic chest pain, dyspnoea, and palpitations may be present, as in non-massive PE.
- Collapse and/or loss of consciousness.
- Sudden cardiovascular instability.
- Hypotension (SBP <90mmHg, or BP fallen >40mmHg).
- Tachycardia.
- Cardiac arrest—PEA is common and has a very poor outlook.

Risk factors

- Immobility
- Recent surgery/fracture
- Pregnancy/postpartum
- Stroke
- Spinal cord injury
- Air travel
- Varicose veins
- Metastatic malignancy
- Pelvic mass
- Chemotherapy
- Thrombotic tendency
- Oral oestrogens

Investigations

- In unstable patients, investigations must be arranged quickly and safely. The gold standard is computed tomography pulmonary angiography (CTPA) scanning which shows filling defects in the central pulmonary circulation.
- Echocardiography is a very useful bedside test which can demonstrate right ventricular (RV) strain and may even visualize the emboli.
- ECG: right ventricular strain pattern, right axis deviation, or tachycardia.
- ABGs: type 1 respiratory failure.

Initial treatment and resuscitation

- ABC.
- High-flow oxygen, regular observations, regular ABGs.

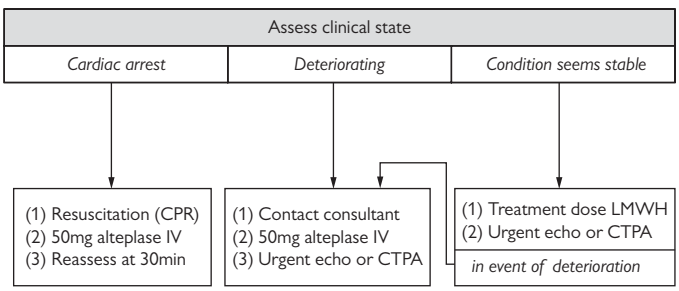
Poor prognostic factors

- Hypotension
- Altered mental state
- Hypoxia
- Malignancy
- Cardiac arrest
- Cardiogenic shock
- RV dilatation
- Brain natriuretic peptide (BNP) elevated.

- Cardiac monitoring is essential—patients with massive PE are prone to arrhythmias (Fig. 1.16).

Treat hypotension

- Consider rapid 0.5–1L crystalloid fluids to improve preload and RV end-diastolic volume.



Comments

1. Massive PE is highly likely if:
   - collapse/hypotension, and
   - unexplained hypoxia, and
   - engorged neck veins, and
   - right ventricular gallop (often)
2. In stable patients where massive PE has been confirmed, iv dose of alteplase is 100mg in 90min (i.e. accelerated myocardial infarction regimen).
3. Thrombolysis is followed by unfractionated heparin after 3 hours, preferably weight-adjusted.
4. A few units have facilities for clot fragmentation via pulmonary artery catheter. Elsewhere, contraindications to thrombolysis should be ignored in life-threatening PE.
5. "Blue light" patients with out-of-hospital cardiac arrest due to PE rarely recover.

Fig. 1.16 Management of patient presenting with probable massive pulmonary embolus (PE).

Reproduced from 'British Thoracic Society guidelines for the management of suspected acute pulmonary embolism', 58, 2003, with permission from BMJ Publishing Group Ltd.

- If hypotension persists, consider insertion of a central line or Swan–Ganz catheter with vascular pressure monitoring to guide fluid administration. Giving more fluids without invasive monitoring risks exacerbating RV stress and may worsen cardiac output.
- Inotropes should be considered early to maintain BP that has not responded to initial fluids.
- First-line agents include dopamine (2.5–10mcg/kg/min) and dobutamine (2–5mcg/kg/min). Noradrenaline may be used additionally, or as an alternative.
- Involve senior colleagues and ITU/CCU teams.

Thrombolysis in massive PE

- Indications include suspected or confirmed PE with cardiovascular instability and significant hypotension or pending cardiac arrest.
- Absolute contraindications to thrombolysis include recent haemorrhage, haemorrhagic stroke, and current GI haemorrhage.
- Relative contraindications include surgery within 7 days, history of peptic ulcer or other GI or urological bleeding, pancreatitis, endocarditis, and prolonged CPR.
- Thrombolysis with alteplase is first-line treatment for massive PE. It may be given on clinical grounds alone if there is concern about imminent cardiac arrest.
- Start alteplase with a 10mg IV bolus over 1–2 minutes, then an infusion of 90mg over 2 hours. In patients <65kg, total dose should be reduced to 1.5mg/kg.
- Alternative agents for thrombolysis include reteplase (unlicensed for PE), streptokinase, and urokinase (less effective in trials, older agents).
- Massive PE in pregnancy requires specialist obstetric involvement. British Thoracic Society guidelines suggest that thrombolysis is advisable in massive PE but not within 6 hours of delivery or in the early postpartum period due to bleeding risks.
- If thrombolysis fails in a deteriorating patient, consider surgical embolectomy.

Anticoagulate

- In massive PE, heparin is generally used after thrombolysis as an infusion without a bolus.
- If thrombolysis is contraindicated or in non-massive PE, treatment with LMWH is standard. UFH is an alternative where rapid reversal of effect is desired.
- LMWH, e.g. enoxaparin: give 1.5mg/kg in a single daily dose. Adjust dose in renal failure to 1mg/kg/day and monitor anti-Xa levels.
- Heparin: start with an IV bolus of 5000–10,000 units then infuse at 400–600 units/kg/day. Monitor APPT aiming to keep the ratio between 1.5 and 2.5.

Once stable

- Start oral anticoagulants (target INR 2.5 in uncomplicated cases) and continue LMWH until INR >2.
- Consider investigating for malignancy or thrombophilia.

1.10 Acute upper gastrointestinal haemorrhage

Background

Acute upper GI haemorrhage is a life-threatening emergency in which clinical diagnosis is based on the history, and early intensive resuscitation with emergency access to an endoscopy service is the key to effective management (see Section 8.5).

Presentation

- Fresh haematemesis or coffee-ground vomit.
- Melaena.
- Collapse.
- Hypovolaemic shock.
- Rectal bleeding.
- Complications of anaemia—chest pain, dyspnoea.

Examination

- HR, BP (including postural), peripheral perfusion—evidence of hypovolaemia and shock.
- Evidence of chronic liver disease—raises suspicion of variceal bleed.
- Rectal examination for melaena.

Investigations

- FBC—anaemia (specifically Hb drop >2g/dL).
- U&Es—increased urea levels (relative to creatinine) due to digested blood, renal function.
- LFT and coagulation screen.
- Group and save sample—haematemesis complicated by shock should initiate a 4–6 unit cross-match.
- ABGs—lactic acidosis indicates poor tissue perfusion.
- CXR—perforation (subdiaphragmatic air) and aspiration.
- ECG—cardiac ischaemia.

Rockall scoring

Used to risk stratify—very effective at predicting risk of:

(a) Death

(b) Re-bleeding (Table 1.2)

Management: massive haemorrhage and Rockall score ≥1

- Immediate management should involve protection of airway from risk of aspiration, fluid resuscitation, correction of coagulopathy, and emergency access to endoscopy.

Table 1.2 Rockall scoring

Variable	0	1	2	3
Age (years)	<60	60–79	>80	
Shock	None	HR >100bpm	SBP <100bpm	
Comorbidity	None		CCF/IHD	Liver/renal failure
			Other major disease	Disseminated malignancy

Reproduced from *Gut*, T A Rockall, R F Logan, H B Devlin, T C Northfield, 'Risk assessment after acute upper gastrointestinal haemorrhage', 38, 3, pp. 316–321, Copyright 1996, with permission from BMJ Publishing Group Ltd.

- Airway protection: avoid supine position due to risk of aspiration. Improve cerebral perfusion by head-down position in hypotension.
- Intubation—required if low GCS.
- Oxygen delivery to maintain saturations ≥95%—care with mask due to vomiting.
- Minimum 2 × large-bore IV cannulae (>18G/green).
- Rapid fluid resuscitation (colloid or crystalloid).

After 1–2L use blood or plasma expanders (if necessary):

- Transfusion of packed red cells if massive bleed, Hb <8g/dL, or Hb <10g/dL with postural hypotension.
- Correct coagulopathy if active bleeding and INR >1.5 or PT >3 seconds prolonged. Use FFP/vitamin K/Beriplex® (Beriplex® and vitamin K if warfarinized).
- Give platelets if count < 50 × 10^9/L and active bleeding.
- Urinary catheter—hourly urine output aiming >0.5mL/kg/hour.
- High dependency monitoring.
- The aim is to resuscitate patients such that they are cardiovascularly stable by the point of endoscopy, i.e. euvolaemic with normal BP (and no postural drop), minimal tachycardia and normal urine output.

Urgent referral for endoscopy:

- Emergency endoscopy is indicated in:
  - Shocked patients (once resuscitated).
  - Continued bleeding, or re-bleeding.
  - Variceal bleeds (known or suspected).
- Endoscopy significantly reduces probability of re-bleeding/surgery/death if there is active bleeding, or a non-bleeding vessel visible. It allows the distinction to be made between variceal and non-variceal bleeding, and gives information regarding the underlying pathology.
- Warn the surgical team pre-endoscopy: performing endoscopy in the operating theatre may be a sensible precaution.

Variceal bleeding

- Involve anaesthetic colleagues early for airway protection.
- Early specialist gastroenterology input.
- IV vasopressin analogue (e.g. terlipressin IV 2g four times a day).
- IV antibiotic therapy: third-generation cephalosporin.
- Early endoscopy—sclerotherapy, injection, and banding.
- Consideration of balloon tamponade (Sengstaken–Blakemore tube) and transjugular intrahepatic portosystemic shunt (TIPSS).

Peptic ulcer disease (post-endoscopy)

- IV proton pump inhibitor—stat dose then 72-hour infusion to reduce risk of re-bleed (e.g. omeprazole 80mg IV stat then 8mg/hour IVI).
- 12–24 hours nil by mouth prior to reintroduction of clear fluids if no signs of re-bleed.
- Discontinue any contributing risk factors.
- *Helicobacter pylori* eradication where required.
- Repeat endoscopy in 4–6 weeks.

Management: Rockall score 0

- Consideration of early discharge if no evidence of ongoing haematemesis or melaena.
- Follow-up out-patient endoscopy.
- Discontinuation of any risk factors (e.g. NSAIDs).

1.11 Acute kidney injury

Background

- Acute kidney injury (AKI; see Section 17.6), previously termed acute renal failure (ARF), occurs in 5–10% of medical admissions.
- It is most often a biochemical diagnosis as evidenced by increasing concentrations of serum urea and creatinine.
- Many patients have few symptoms, but may report reduced urine output, general malaise, and fatigue.

Causes

Pre-renal

- Hypovolaemia, shock, decreased cardiac output.
- Renovascular disease, such as renal artery stenosis, or hypoxic injury through vessel clamping during aneurysm surgery.
- Iatrogenic agents interfering with renal blood flow autoregulation.

Renal

- Glomerulonephritis.
- Tubular damage—including rhabdomyolysis, ischaemia, myeloma (cast nephropathy), hypercalcaemia, nephrotoxins.
- Interstitial renal disease—infection, infiltrations, drugs.

Post-renal

- Bladder or ureteric obstruction—prostatism, stones, clots, tumours, retroperitoneal fibrosis.

History and examination

- Take a careful history, particularly of medications which have recently been started or doses amended.
- Ask about onset of symptoms: is this acute, subacute, or a first presentation of chronic renal failure? A baseline creatinine level is very helpful (contact their GP).
- Fluid status: check BP, JVP, oedema, bibasal crepitations. Is the patient hypovolaemic, euvolaemic, or overloaded? Document this in the notes.
- Features of systemic disease, such as systemic lupus erythematosus or vasculitis.
- Abdominal examination: renal mass or renal angle tenderness.
- Is there urinary retention? Catheterize if any doubt.
- Conscious level and general condition: is the patient critically unwell with multi-organ failure and new-onset cognitive dysfunction? Consider ITU referral.

Priorities of management

Investigations

- Blood tests; U&Es, bicarbonate, calcium, CRP, creatine kinase (CK), FBC, and coagulation are essential. LFT, troponin, erythrocyte sedimentation rate (ESR), myeloma screen, blood cultures, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), glomerular basement membrane (GBM), and complement levels may also be indicated.
- Urgent ultrasound of the urinary tract: excludes many obstructive or post-renal causes.
- Urinalysis: heavy protein and blood ('active' urinary sediment) may reflect a glomerular cause. Nitrites and leucocytes indicate possible infection.
- Identify and treat any precipitating cause. Common precipitants include infection; nephrotoxic medication such as ACE inhibitors, diuretics, NSAIDs, antibiotics, and chemotherapeutics; surgery or cardiac events with hypoperfusion. Do a CXR.
- What is the underlying renal cause? Many patients with infection, hypovolaemia, and AKI develop acute tubular necrosis. Where the renal diagnosis is unclear, or where renal function does not recover, consider renal biopsy.

Practical steps: fluids and medications

- Insert urinary catheter and keep strict hourly input/output charts.
- Withhold nephrotoxins such as ACE inhibitors, diuretics, and NSAIDs during the acute illness. These medications can be reviewed prior to discharge.
- Be cautious with prescribing—antibiotic doses may need to be adjusted.
- If the patient is clinically hypovolaemic, rehydrate with Normal saline (try 1L over 4–8 hours and reassess). Profoundly hypovolaemic patients may benefit from more aggressive initial rehydration. In all patients, particularly those with cardiac failure, repeated review of volume status prevents significant fluid overload.
- Patients with fluid overload should not be given additional fluid, particularly if this is compromising respiratory status. Diuretics should be used with extreme caution in this situation: involve senior or specialist colleagues.

Practical steps: management of potassium

- Hyperkalaemia results from acidosis and reduced glomerular filtration rate: all patients with AKI are at risk.
- ECG: check for hyperkalaemic changes. If present, urgent action is required. Medical management of moderate hyperkalaemia (K >6–6.5mmol/L) includes:
  - Calcium gluconate—10mL of 10% given over 2–3 minutes stabilizes the myocardium. Buys time to prepare the next step.
  - Insulin and dextrose: give 10–15 units of insulin in 50mL 50% dextrose over 30 minutes (and repeat if necessary).
  - Calcium resonium 15mg three times a day orally—works over several days, unpleasant taste, constipating effect (give laxatives concurrently).
  - Acidosis drives potassium out of cells. If present consider treating with sodium bicarbonate 1g three times a day PO.
- Severe hyperkalaemia with K >7mmol/L and resistant to medical management requires renal replacement therapy.

Dialysis or haemofiltration

- Life-threatening fluid overload or hyperkalaemia.
- Unresolving AKI with uraemic symptoms.
- Requires placement of a dialysis line and specialist services.
- Ensure platelet count and coagulation are satisfactory prior to line placement.
- Generally, haemodialysis (intermittent therapy) is provided by nephrological services, and is used if patients are cardiovascularly stable with single-organ failure. If multiple-organ failure, or unstable, consider haemofiltration (continuous therapy)—usually provided in an ITU setting.

1.12 Coma

Background

- Coma refers to a state of 'unrousable unresponsiveness' and most usually and perhaps accurately refers to a patient who scores as '3' on the Glasgow Coma Scale (GCS; see Section 14.2).
- The approach to the patient in a comatose state also applies to patients with a diminution of responsiveness, corresponding with a reduced GCS score, and imprecisely described as lethargy, stupor, or obtundation.
- Coma represents both an acute medical emergency and a considerable challenge to diagnose the underlying cause. Immediate management should focus on resuscitation and empirical treatment at the same time as looking for clues as to the specific aetiology.

Causes

Can be crudely classified as:

• Metabolic	• Toxic
• Infective	• Structural

Coma may present with or without focal brainstem signs, lateralizing cerebral signs, or meningism. Toxic and metabolic causes rarely have such lateralizing signs, while infective and structural precipitants do, due to brainstem or cerebral dysfunction. Meningism suggests meningitis, encephalitis, or subarachnoid haemorrhage (SAH).

Usually without lateralizing/focal signs

- Metabolic causes such as hypo/hyperglycaemia (diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS), previously known as HONK), acid–base disturbances, electrolyte disturbances (usually Na or Ca), renal failure (uraemia), liver failure.
- Toxic causes such as alcohol, opiates, benzodiazepines, tricyclic antidepressants, neuroleptic medications, lithium, barbiturates, carbon monoxide.
- Hypoxia, CO_2 narcosis (retention, e.g. in COPD).
- Endocrine causes—hypothyroidism, Addisonian crisis, hypopituitarism.
- Temperature—hypothermia or malignant hyperthermia.
- Epilepsy.
- Hypertensive emergency with encephalopathy.
- Profound hypoperfusion secondary to systemic sepsis.

Usually with lateralizing or focal signs

- Ischaemic or haemorrhagic stroke.
- Space-occupying lesions: tumour, haematoma, or abscess—either within the brainstem or with sufficient mass effect to compress it.

With meningism

- Meningitis or encephalitis.
- SAH.

Immediate management

Prompt resuscitation, regardless of cause.

- ABC, O_2 (caution if CO_2 retention suspected).
- Any suggestion of 'brainstem' breathing patterns requires early involvement of critical care and consideration of early intubation.
- IV access.
- Capillary blood glucose.
- Circulatory support with IV fluids.
- If possibility of trauma, stabilize the cervical spine.
- Control any seizure activity—beware of over-sedation.
- Consider giving IV glucose to correct any hypoglycaemia, though there is the potential for this to precipitate Wernicke encephalopathy in malnourished patients. In this case, IV thiamine (100–200mg, or as Pabrinex®) should be given first.
- Naloxone (IV/IM/endotracheal tube (ET)) should be given for suspected opiate toxicity (as a slow titration series of boluses up to a maximum total dose of 10mg). If effective, a maintenance infusion may be required: give 2/3 of the initial dose required (to achieve reversal) per hour.
- Flumazenil should be given if there is a probability of benzodiazepine intoxication and breathing is compromised, but not where there is a suspicion of a mixed overdose. It may precipitate seizures, especially in tricyclic antidepressant overdose, and is contraindicated in epileptics who have received prolonged benzodiazepine therapy. Initial dose 200mcg given over 15 seconds then further 100mcg doses at 1-minute intervals up to a maximum of 1mg.

Initial investigations

- ABGs, U&Es, LFT, calcium, phosphate, clotting, CRP, ESR.
- Paracetamol and salicylate levels, urine toxicology, ethanol.
- Septic screen: CXR, blood culture, urine culture, serology, (malaria film).
- Further imaging and investigations after history, examination, and empirical management.

History

This is often lacking but a brief and pertinent history can greatly inform subsequent examination, investigation, and management by narrowing the differential diagnosis. Family members, witnesses, and ambulance crews are all likely sources. Key lines of enquiry include:

- **Timecourse**—abrupt suggests a vascular event such as SAH or seizure, gradual may suggest structural lesion, fluctuating suggests recurrent seizures, metabolic causes, subdural bleed.
- **Preceding symptoms/signs/illnesses**—focal signs or symptoms, weakness, visual symptoms, fever, nausea, vomiting, headaches, confusion, delirium.
- **Past medical history**—is there a MedicAlert bracelet? Any recent falls, previous stroke, or TIA? Any old notes available? Electronic records can be particularly useful. Any diabetes, adrenal insufficiency, epilepsy? Recent travel?
- **Psychiatric history**—any suggestion of depression, previous suicide attempts, suspicious circumstances, or a note left?
- **Drug history**—prescription drugs, illicit drugs, alcohol, toxins?

General examination

- **Core temperature**—hyperthermia usually suggests infection but may also occur with anticholinergic medications, heatstroke, or diencephalic lesions. Hypothermia can be due to exposure, hypothalamic dysfunction, hypothyroidism, adrenal insufficiency, sepsis, alcohol intoxication.
- **BP**—extreme hypertension suggests hypertensive encephalopathy, intracerebral haemorrhage, or posterior reversible encephalopathy syndrome (PRES).

Hypotension can lead to anoxia and cerebral ischaemia and thus coma. Cardiac failure, sepsis, hypovolaemia, adrenal insufficiency and drugs should be considered as precipitants.

- **Cardiac**—HR, rhythm, ECG may suggest an underlying dysrhythmic cause for poor cerebral perfusion.
- **Respiratory pattern**—hypoventilation can suggest drug intoxication, hyperventilation may be a feature of metabolic abnormalities, such as Kussmaul breathing in acidosis. Specific breathing patterns can be seen in brainstem lesions.
- **Breath**—alcohol, ketosis, hepatic foetor, uraemia.
- **Skin**—look for signs of head trauma, such as periorbital bruising, Battle's sign (bruising over the mastoid), or blood in the ears suggesting skull base trauma. Rashes can suggest meningococcal or other infection or coagulopathic conditions such as DIC. Are there signs of liver or renal disease? Intravenous drug users may have track marks. Sweating is common in hypoglycaemia and sepsis. Cherry red mucous membranes suggest carbon monoxide poisoning. Fingerprick marks suggest diabetes on insulin.
- **Chest**—breath sounds, consolidation, rub, wheeze.
- **Heart**—murmurs may suggest endocarditis.
- **Abdomen**—organomegaly. Peritonism suggestive of bleed, perforation, aneurysmal rupture.
- **Chronic disease**—stigmata of alcoholism, liver disease, diabetes, myxoedema.
- **Infection**—any local focus of infection.
- **Pupils**—may localize intracranial lesions. Pinpoint pupils suggest opiate toxicity.
- **Fundi**—papilloedema suggests, but is not required for, raised intracranial pressure (ICP). May also see diabetic or hypertensive changes.
- **Meningism**—neck stiffness, photophobia, etc.

Neurological examination

Full discussion of a comprehensive neurological examination is beyond the scope of this chapter but the fundamental elements to consider are outlined. Remember to look for any *change* in neurological status.

Conscious level

- Establish GCS score and continue to monitor along with vital signs.

Motor responses

- Muscle tone.
- Spontaneous and elicited movements.
- Reflexes.
- Asymmetry—lateralizing lesion.
- Decorticate or decerebrate posturing.
- Myoclonus/asterixis—suggests metabolic aetiology.
- Cranial nerves—localizing lesion.

Brainstem function

- Pupillary reactivity (usually reactive in metabolic coma).
- Corneal reflex.
- Eye position/spontaneous movements.
- Doll's head manoeuvre/vestibulo-ocular response.
- Swallowing.
- Respiratory pattern.

Brainstem lesions may be structural (intrinsic or extrinsic compression) or due to metabolic dysfunction. The latter tends to have a better prognosis; the former is more likely to give focal brainstem dysfunction.

Further management

If brainstem function is intact, proceed to CT head. If a potentially operable lesion is identified (e.g. subdural, subarachnoid/intracerebral bleed, or ischaemic stroke with oedema), then refer to neurosurgery. A lumbar puncture (LP) should be considered if the CT is normal to exclude infection (although if a high degree of suspicion exists, proceed to treat for meningitis).

If brainstem function is compromised, then compressive brain shift should be considered and treatment for suspected raised ICP, such as mannitol and surgical referral, instigated (see Section 1.13). An urgent CT should be performed when able, and LP, again, considered if the CT is normal. An MRI may be helpful if the CT/LP fail to identify a cause for coma.

At all stages, seek senior and specialist input where appropriate.

1.13 Traumatic brain injury

Background

Head injury, or traumatic brain injury (TBI), is a significant cause of mortality and lifelong disablement in young and middle-aged patients (see Section 13.3).

Approach

- Patients with head injury often have other injuries (e.g. fractures, pneumothorax, myocardial contusion, internal haemorrhage) requiring involvement of many specialties.
- These injuries can contribute to hypoxia and hypotension, which are poor prognostic markers.

Hospital care

- 'ABC' and resuscitation as needed.
- Disability: examine thoroughly to assess extent of the injuries, including neurological assessment and GCS score.
- Observations—take baseline and monitor regularly.
- Investigations: ABGs, glucose, FBC, U&Es, coagulation, and blood alcohol concentration. Urinary toxicology.
- Neuroimaging with CT scanning in all patients with GCS score <14 or if clinical deterioration. Urgent CT is also recommended in patients with focal neurological abnormalities, coagulopathy, suspected skull fracture, or amnesia. CT will identify an intracranial haematoma, cerebral oedema, and skull fractures. Image the spine with CT or X-rays.
- Admit all patients who are difficult to assess, with neurological signs or symptoms of raised ICP.

Neurosurgical input

- Contact neurosurgeons early.
- Operative therapy is recommended for patients with:
  - Large extradural haematoma (>30mL volume), or a smaller haematoma associated with reduced GCS score or pupillary abnormalities.
  - Subdural haematoma >10mm in diameter or with evidence of midline shift.
  - Cerebral haemorrhage involving the posterior fossa with mass effect, or in other areas if large and GCS score of 6–8.
  - Depressed open skull fracture with haemorrhage or pneumocephalus.
  - Base of skull fracture or cerebrospinal fluid (CSF) leak.

Intensive care

- Patients benefit from management in a specialized neurocritical care department with a multidisciplinary approach.
- Principles of management are to avoid further brain injury by treating hypoxia, seizures, and raised ICP and by maintaining cerebral perfusion.
- Airway management with intubation, sedation, and ventilation is often required. Ventilate all patients with GCS score <8, PaO_2 <9kPa on air, or $PaCO_2$ <3.5 or >6kPa, and consider ventilating patients with seizures and reducing GCS score.
- Check electrolytes and glucose and correct as required. Tight glycaemic control may improve outcomes.
- Consider prophylaxis for deep vein thrombosis (DVT).
- Nutritional support is important.

Seizures

- In severe head injury, treat prophylactically for seizures: phenytoin is ideal. Monitor carefully for seizure activity and for non-convulsive seizures and treat aggressively.

Neuroprotective treatments

- Induced hypothermia can reduce ICP and improve long-term neurological function and has been employed in the clinical trial setting in patients with TBI.
- Glucocorticoids result in a worse outcome after TBI: avoid (unless indicated for coexistent conditions).

Raised intracranial pressure

- Raised ICP may occur following intracranial haemorrhage or TBI. Other causes include intracranial tumour, ischaemic stroke, hydrocephalus, venous sinus thrombosis, and hepatic encephalopathy. Prompt identification and treatment are essential to improve survival.

Clinical features

- Headache with vomiting.
- Reduced consciousness. Listless, irritable behaviour.
- Papilloedema.
- False localizing cranial nerve signs may be present.

Signs suggesting impending herniation—need *urgent* treatment

- Unilaterally or bilaterally fixed and dilated pupils.
- Decerebrate posturing.
- Cushing triad (bradycardia, respiratory depression, hypertension) indicates likely brainstem compression and impending herniation.

Management of raised ICP

- Treat the underlying cause.
- The insertion of an intraventricular catheter allows monitoring of ICP. In adults, an ICP <15mmHg is normal: >20mmHg is considered raised and requires treatment.
- Patients with GCS score <8 with signs suggestive of impending herniation need urgent treatment.
- Elevate the head of the bed to 20 –30°. Keep the neck in the neutral position to optimize venous drainage.
- Osmotic therapy (e.g. mannitol).
- Dexamethasone is useful to reduce cerebral oedema in patients with intracranial tumours.
- Surgical decompressive craniectomy removes part of the skull to reduce ICP.
- Avoid giving excess fluid; aim for euvolaemia. Fluid restriction to 1.5L per day is occasionally required.
- Treat pyrexia and seizures aggressively.
- Hyperventilation reduces CO_2 levels, promoting cerebral vasoconstriction and reducing ICP. Unfortunately it can also lead to cerebral ischaemia and so must be undertaken with caution.
- Sedation is thought to reduce metabolic demands, and hence reduce ICP. In practice, most patients with severe TBI who are ventilated will require some sedation. Propofol or barbiturates are recommended.

Prognosis after severe TBI

- 30% die.
- 45% survive with disability.
- 25% achieve independence.

Poor prognostic factors

• Increasing age	• GCS score at presentation
• Multiple pre-existing medical conditions	• Pupillary function
• Multiple associated injuries	• Hypotension
• Raised ICP	• Hypoxaemia
• Severity of the brain injury	• Bleeding diathesis
• CT findings—midline shift, SAH	• Pyrexia

1.14 Status epilepticus

Definition

- Status epilepticus is a potentially fatal medical emergency requiring prompt treatment to avoid both neurological and metabolic complications.
- It is defined as continuous seizures for >30 minutes or failure to regain full consciousness between seizures.

Presentation

- Generalized tonic–clonic seizures.
- Complex partial seizures.
- Non-convulsive status—confusion, psychosis, automatisms, and in known epileptics a prolonged post-ictal phase.
- Continuing symptoms for >30 minutes despite initial intervention with benzodiazepines.

Investigations

- Blood glucose measurement to detect hypoglycaemia.
- U&Es, calcium, and magnesium to detect potential reversible causes.
- Blood levels of antiepileptic medications for compliance review.
- Toxicology screen if possible.
- Prolactin levels may be useful in the differential of non-epileptiform seizures.
- ABGs—respiratory failure prompting treatment escalation, lactic acidosis.
- CXR for signs of aspiration or causative infection.
- Electroencephalogram (EEG)—differential diagnosis and distinguish non-epileptiform seizures.

Management

- Immediate management should involve the protection of the patient from risks (injury, aspiration, and hypoxia) and correction of reversible causes.
- Involve senior colleagues early, including anaesthetists for airway protection.
- Airway protection: recovery position, nasopharyngeal or Guedel airway (do not force between clenched teeth).
- Oxygen delivery via mask to maintain saturations ≥95%.
- Benzodiazepine—current recommendation is IV lorazepam 1mg IV in increments to a maximum of 4mg over 10 minutes (care with patients of low weight and known type II respiratory failure). Use of rectal diazepam is not recommended in hospital settings due to slow rate of absorption.
- IV phenytoin should be used if these measures fail to control seizures within 30 minutes—give loading dose of 18mg/kg at a rate of 50mg per minute.
- Continue phenytoin at 100mg IV 6–8-hourly.
- Patients should be cardiac monitored throughout all phenytoin infusions.
- Failure to control seizures despite the outlined management and certainly if seizures are still evident after 60 minutes, prompt referral for anaesthetic review should be made. The patient may require intubation, sedation, and paralysing in the ITU setting.
- Once control of seizures has been gained, investigation for potential cause should be undertaken.
- Repeated and regular clinical assessment is warranted in a monitored higher-level dependency setting.

Further management and investigation

- Hypoglycaemia should be corrected with IV glucose (100mL of 10% dextrose).
- Consideration of IV thiamine (Pabrinex®) in patients suspected of having malnutrition (e.g. alcohol abuse)—prior to correction of hypoglycaemia.
- Hyponatraemia: correct if severe (usually <115mmol/L to cause seizures)—exercise caution with rate/degree of correction (see Section 7.21).
- Cerebral infections—consider meningitis and/or encephalitis if previous history suggestive and treat initially with high-dose IV medications as per local policy (e.g. 2g IV cefotaxime ± 10mg/kg IV aciclovir).
- CT head to detect cause (haemorrhage, cerebrovascular accident (CVA), space-occupying lesion, raised ICP).
- Lumbar puncture if symptoms/signs suggestive of intracerebral infection (and no contraindication on CT).
- IV fluids for rehydration and maintenance: remember that excessive fluid losses occur during active seizures.
- Continuation of patient's usual anti-epileptic medications (oral or nasogastric).
- Referral to specialist neurology team for inpatient review and follow-up on discharge from hospital.

Non-convulsive and non-epileptiform status

- Non-convulsive status is less common then generalized tonic–clonic seizures.
- Treatment should include use of EEG for diagnosis, benzodiazepines, and early specialist input.
- Non-epileptiform seizures (pseudo-seizures) should be considered in patients with atypical limb movements, active resistance to passive movement, absence of metabolic complications, gaze aversion, and in the absence of a post-ictal phase.
- Early specialist referral and EEG are beneficial in this diagnosis—if any doubt, treat as status epilepticus initially.

1.15 Adrenal crisis

Background

- Acute adrenal crisis can occur either in those with known disease on maintenance steroid therapy, or in those with subclinical disease not yet diagnosed.
- Acute adrenal crisis can result from stressful precipitants such as infection, surgery, trauma, or other systemic disease.
- Such a crisis may also be the initial presentation and constitutes an acute life-threatening medical emergency, in which treatment should be instigated on clinical suspicion.
- Suspicion should be raised in any critically ill patient with no clear alternative diagnosis.

Presentation

Often varied and non-specific. The trigger for adrenal crisis (e.g. pneumonia) may be the most apparent feature:

- Hypotension and cardiovascular shock.
- Postural symptoms.
- Nausea and vomiting.
- Abdominal pain.
- Dehydration.
- Anorexia, weight loss, fatigue, myalgia.
- Diarrhoea.
- Psychiatric features.
- Hypoglycaemia.
- Hyponatraemia and hyperkalaemia.
- Hyperpigmentation in chronic primary disease.

Aetiology of adrenal insufficiency

- Autoimmune.
- Tuberculosis.
- Malignant adrenal secondaries.
- Adrenal haemorrhage (e.g. meningococcal septicaemia—Waterhouse–Friderichsen syndrome).
- Traumatic shock.
- Fungal infection.
- Hypopituitarism.
- Drugs (metyrapone, aminoglutethimide).
- Adrenoleucodystrophy.
- Congenital adrenal hyperplasia.
- Familial glucocorticoid deficiency.

Crisis precipitants in stable disease

- Infection and sepsis.
- Trauma.
- Severe burns.
- Anaesthesia and surgery (especially if there is a failure to continue or increase steroid therapy to cover the period of physiological stress).
- Drugs (ketoconazole, etomidate, rifampicin, phenytoin, phenobarbitone).
- Liver failure.
- Later stages of pregnancy and parturition.

Investigations

- U&Es: hyponatraemia, hyperkalaemia, dehydration (may be less pronounced in secondary disease with preserved mineralocorticoid activity).
- FBC: normocytic anaemia.
- Glucose: hypoglycaemia.
- Calcium: elevated.
- Cortisol: note 'normal' level in illness should be ~1000nmol/L.
- ACTH: High or low, depending on the cause of adrenal insufficiency.
- ABGs: metabolic acidosis.
- Full septic screen including CXR (in case of past tuberculosis).

Acute management

- Treat on clinical suspicion.
- Resuscitation ('ABC').
- Involve intensive care and manage in high dependency setting with CVP monitoring and catheter for urine output.
- Fluid resuscitation for shock—may require several litres of 0.9% saline but exercise caution if chronic hyponatraemia as rapid correction can precipitate central pontine myelinolysis. Seek endocrine advice if severe hyponatraemia at presentation.
- Carefully monitor U&Es and fluid balance.
- Hydrocortisone 100mg IV/IM bolus and then 150–400mg/24 hours in divided doses.
- Correct hypoglycaemia.
- Investigate and treat precipitant (such as infection). Broad-spectrum antibiotic cover may be indicated.

Subsequent management

- A full endocrine review of the likely aetiology is mandated including paired ACTH and cortisol, Synacthen testing, adrenal autoantibodies, etc. (see Section 7.13).
- Steroid replacement can be transitioned to oral hydrocortisone once stable at a minimum of double replacement dose (i.e. 20/10/10mg daily). This can then be weaned under supervision to a maintenance regimen of 10/5/5mg daily as tolerated. At total daily hydrocortisone doses of <40mg, fludrocortisone must be added in primary adrenal disease (50–200mcg daily) to provide sufficient mineralocorticoid activity.
- Steroid sick day rules should be reviewed in patients with existing disease and taught to newly diagnosed patients.
- Endocrine follow-up must be arranged.

1.16 Thyroid emergencies

Background

Thyroid disease usually manifests insidiously and when symptoms develop, there is ample time to make the diagnosis before the situation becomes critical. There are, however, occasions when dysthyroid states present as acute medical emergencies, requiring prompt recognition and action.

Thyroid storm/thyrotoxic crisis

See Section 7.3.

Myxoedema/myxoedema coma

- This represents severe hypothyroidism and can occur in the context of severe long-standing disease with inadequate treatment or be precipitated by an acute event.
- Coma and ultimately death may ensue.
- Collateral history to establish previous thyroid status, progressive symptoms, and potential precipitants is important.
- Other causes of coma should be considered.

Presentation

Neurological features

- Altered mental status/confusion.
- Lethargy.
- Decreased conscious level, coma.
- Psychosis, depression.
- Encephalopathy, seizures.
- Cerebellar ataxia.
- Slow-relaxing reflexes (symmetrical).

Other features

- Cardiac failure, pericardial effusion.
- Bradycardia, hypotension.
- Hypothermia.
- Hypoglycaemia, hyponatraemia.
- Hypoventilation (hypoxia and hypercapnia).
- Intestinal obstruction.

Precipitants

- Any untreated cause of hypothyroidism.
- Drugs (especially sedatives, opiates).
- Cold exposure.
- Trauma, infection, stroke.

Investigations

- U&Es, glucose, FBC, CK, thyroid stimulating hormone (TSH) and free thyroxine (FT4), cortisol, ABGs.
- Septic screen, CXR, ECG.

Management

- Do not wait for thyroid function results.
- Treat any precipitants (e.g. antibiotics after culture).
- Support ventilation/circulation (HDU/ITU) as appropriate.
- Correct hypoglycaemia/hyponatraemia.
- Correct core temperature (by 0.5°C/hour).
- Cardiac monitoring.
- Hydrocortisone 50–100mg IV 6–8-hourly until adrenal sufficiency demonstrated.
- Thyroid hormone replacement as per local specialist endocrine advice—e.g. 300–500mcg levothyroxine (L-T4) NG/IV as a bolus then 50–100mcg daily. If no improvement within 48 hours, liothyronine (L-T3) can be given IV at 10–25mcg/8 hours.

1.17 Acute poisoning

Background

Accounting for 10% of hospital admissions, acute poisoning is an important cause of coma and cardiac arrest, especially in younger people. It may occur both deliberately and accidentally, with many different routes of exposure.

Despite the many and varied potential poisons, initial management follows the same 'ABC' approach, stabilize the patient, prevent further drug absorption, and increase toxin clearance.

Routes of exposure

- Inhalation
- Ingestion
- Absorption
- Injection (IV, IM, SC)

Approach to management

- Personal safety is extremely important to avoid self-exposure.
- If the patient is unconscious, obtain a collateral history from friends or relatives.
- **A**irway: clear and maintain the airway, use adjuncts as necessary, and consider endotracheal intubation if GCS score <8 (aspiration risk).
- **B**reathing: if absent or inadequate use bag-mask ventilation. Avoid mouth- to-mouth respiration due to risk of contamination. Administer O_2 to maintain saturations 95%. Check ABGs.
- **C**irculation: cardiac compressions and full advanced life support if indicated. Hypotension requires fluid resuscitation with inotropic support if failure to respond. Cardiac monitoring should be commenced. Send routine bloods including paracetamol and salicylate levels.
- **D**: reduced GCS score should warrant ITU review. Check blood glucose.
- **E**: examine for specific signs related to individual poisons.

Prevention of further drug absorption

- Remove patient from the source.
- Activated charcoal (50g) should be given to fully conscious patients within 1 hour of ingestion of a poison known to be absorbed by charcoal. Repeated doses may be helpful.
- Gastric lavage followed by activated charcoal may be considered within 1 hour of ingestion for intubated patients.

Increased elimination

- Urine alkalinization by giving IV 1.4% sodium bicarbonate may be used in severe salicylate poisoning (see Section 5.8).
- Haemodialysis may be used for lithium, methanol, ethylene glycol, and salicylate poisoning.
- Haemoperfusion is rarely required.

Specific antidotes/therapies

The more common specific antidotes are listed as follows. This list is not exhaustive and each individual case should be reviewed on its own merits:

- Naloxone: opioids—400mcg IV with repeated doses to max. 10mg if no response. Caution: short half-life so may require further doses or infusion. (A rough guide is to use 2/3 of the naloxone dose needed initially as an infusion per hour, titrating according to response.)
- Flumazenil: benzodiazepine—200mcg IV with repeated doses (severe cases only). Should not be given in mixed overdoses or as a diagnostic test.
- N-acetylcysteine: paracetamol—IV infusion: first dose 150mg/kg in 200mL 5% dextrose over 15 minutes, then 50mg/kg in 500mL over 4 hours, followed by 100mg/kg in 1L over 16 hours. Repeated third doses may be required. Use nomograms to assess whether serum paracetamol level requires treating (see Section 5.7).
- Oxygen: carbon monoxide poisoning (paraquat lung injury is worsened by high oxygen concentrations) (see Section 5.11).
- Vitamin K and Beriplex®: warfarin.
- Ethanol: methanol/ethylene glycol (see Section 5.12).
- Glucagon: beta-blockers—5–10mg IV (may precipitate severe vomiting).
- Digoxin antibodies: severe digoxin toxicity (see Section 5.10).
- Sodium bicarbonate: tricyclic antidepressants with cardiac arrhythmia (see Section 5.13).

Follow-up

- Patients presenting with deliberate self-poisoning should be referred for a psychiatric review.

Further information

- MIMS Colour Index, British National Formulary (BNF), and Data Sheet Compendium may aid in the identification of tablets.
- UK National Poisons Information Service (NPIS) offers 24-hour phone advice to clinicians: Telephone: 0844 892 0111.
- TOXBASE® (<http://www.toxbase.org>) is an Internet database of specific poisons, available in the UK.

1.18 Burns

Background

- Burns constitute a significant cause of accidental morbidity and, when severe, mortality.
- Whilst emergency medicine departments, intensivists, and plastic surgeons shoulder much of the burden of care for these patients, there is a role for the physician to play in managing the multisystem sequelae of moderate and severe burns.
- Full use of appropriate specialist teams should be sought and referral to a tertiary burns unit made in severe cases.
- This section focuses on thermal burns. Chemical or electrical burns require expert input.

Assessment of patient

Airway

- Be vigilant for airway burns from inhalation of hot gases, which can lead to progressive or delayed upper airway obstruction. This represents the most common cause of death in burn victims and is present in 2/3 of patients with >70% burns.
- Signs include visible burns peri-orally, oedema or blistering of the oropharynx, hoarseness, dysphagia, stridor, singeing of facial or nasal hair, and soot-staining of the oral and nasal cavities. Such patients may be obtunded.
- Flexible laryngoscopy or bronchoscopy should be considered for assessment and to guide placement of airway adjuncts or intubation, which may well be life-saving if done early. Anaesthetic input is valuable in this situation. The cervical spine should be assessed and protected as appropriate if injury is suspected.

Breathing

- Severe burns may restrict chest wall movement and there may be coexistent rib injuries or pneumothorax. Decompression may prove necessary.
- Carbon monoxide (CO) poisoning (cherry-red skin, raised carboxyhaemoglobin) or inhalational cyanide toxicity (dizziness, headaches, seizures, raised lactate) should be suspected. CO poisoning mandates the use of high-flow O_2 via a non-rebreathe mask and the consideration of hyperbaric O_2 therapy. Suspected cyanide toxicity should precipitate specialist referral. Treatment options include sodium thiosulphate and hydroxycobalamin.
- ABG analysis, peak flow readings, and chest radiography may inform management. Pulse oximetry should be interpreted with caution in the context of inhalational injury. Alongside supplementary O_2 and airway adjuncts, bronchodilators may have a role. Where mechanical ventilation is required, low tidal volumes should be used to reduce mechanical lung injury.

Circulation

- Fluid resuscitation is paramount in management of burns patients. Hypovolaemic shock results from large fluid shifts due to increased capillary permeability and impaired cardiac function. Rapid repletion of intravascular volume is crucial for maintenance of end-organ perfusion and function. Losses can be severe but over-correction can result in pulmonary oedema and increased risk of compartment syndrome. As such, arterial line monitoring and catheterization for accurate fluid balance assessment is mandatory. A urine output of 0.5mL/kg/hour is optimal. Two large-bore IV cannulae or a central line should be sited and resuscitation commenced with 0.9% saline or Hartmann solution. Colloid has not been proven to be superior.
- A number of calculators for fluid requirements in burns exist, and hospitals may have local guidelines. The commonly used Parkland formula advises 4 × (weight in kg) × (% total body surface area affected) mL Hartmann per 24 hours, with half to be given in the first 8 hours. Changes in rate of infusion should be minimized to avoid vascular collapse and major fluid shifts but adjust input according to vital signs, urine output, and fluid status.
- It must be remembered that any suggested regimen is only a starting point; age, comorbidities, and severity of burn and injury will affect requirements. Electrolytes must be monitored. Serum lactate may be a useful monitoring tool—elevated lactate implies insufficient organ perfusion.
- Cautious blood transfusion may be indicated in severe burns, e.g. where there is a risk of acute coronary syndrome. Haemoconcentration is frequently evident in the early stages.

Assessment of circumstances

A collateral history should be taken alongside immediate resuscitation measures and should address:

- Material burned (chemical/textile/plastic)?
- Was there an explosion (blast injury)?
- Was there associated trauma?
- Duration of exposure.
- Confinement in enclosed space (risk of CO poisoning).
- Any loss of consciousness.
- Past medical history.
- Coexisting use of alcohol or drugs.

Assessment of burn severity and extent

Burn depth

Assessment informs the need for surgical intervention.

Superficial burns involve the epidermal layer of the skin and manifest as painful blanching erythema. They usually heal in a matter of days without significant scarring.

Superficial partial-thickness burns involve the epidermis and superficial dermis, are painful, erythematous, and may not blanch under pressure. Often associated with blistering, they heal in weeks not days, although scarring is again unusual.

Deep partial-thickness burns extend to the deeper dermis and are often insensate except under pressure, do not blanch and have extensive blistering. They usually scar, sometimes extensively, and take several weeks to heal.

Full-thickness burns extend through the dermis, are usually painless, and can appear white or grey/black with no blanching. They will not heal without plastic surgery intervention.

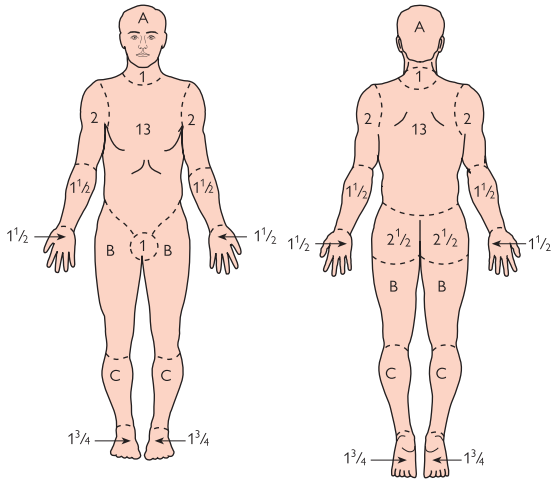
Fourth-degree burns extend into underlying tissues and are life-threatening.

Burn area

Assessment of the surface area involved informs fluid resuscitation, influencing the magnitude of the inflammatory response and subsequent fluid shift. A variety of ways of estimating total body surface area (TBSA) exist, the most familiar of which are the rule of 'nines', which apportions 9% for the head, and each arm, 18% for the each leg and the front and back of the trunk, and 1% for the perineum, and the Lund and Browder chart (Fig. 1.17).

Burn treatment

- Burned clothing, jewellery, and foreign material should be removed.
- Wounds should be irrigated. Water is acceptable, disinfectants should be avoided. Cool fluid may minimize the zone of injury but excessive exposure to very cold solutions can exacerbate tissue



Relative percentage of body surface area affected by growth

Area	Age 0	1	5	10	15	Adult
A: half of head	9½	8½	6½	5½	4½	3½
B: half of thigh	2¾	3¼	4	4¼	4½	4¾
C: half of leg	2½	2½	2¾	3	3¼	3½

Fig. 1.17 Lund and Browder chart for calculating the percentage of body surface area.

Reproduced from *British Medical Journal*, 'ABC of burns: Initial management of a major burn: II—assessment and resuscitation', Shehan Hettiaratchy and Remo Papini, 529, p. 101, 2004, with permission from BMJ Publishing Group Ltd.

damage and precipitate systemic shock. Some authors advocate the use of warmed fluids to avoid this.

- Blisters should be left intact.
- The burn site should be protected with cling-film or dry sterile sheets. More extensive dressing should be held until after assessment by a specialist.
- Escharotomy may be required in compartment syndrome or constriction of the thorax by circumferential full-thickness burns.
- Partial-thickness burns may be dressed with a variety of biological or synthetic dressings, or with silver sulfadiazine cream. Full-thickness burns should be assessed for early split-skin grafting.

Adjunctive measures

- Analgesia is important. Large doses of IV opiates may be required, with appropriate anti-emetic cover. There may be a case for anxiolytics such as benzodiazepines.
- Tetanus status should be established and immunization administered accordingly.
- Antibiotic prophylaxis is indicated in partial and full-thickness burns. In addition to the obvious portal of entry for pathogenic organisms, burns patients are rendered immunosuppressed. Topical antibiotics can be used at burn sites in addition to systemic administration.
- The gross elevation of stress hormones predisposes to hyperglycaemia and insulin administration should be considered.
- Beta-blockade can be used judiciously to mitigate tachycardia and the catabolic effect of severe burns.

Special circumstances

Electrical burns can cause deep tissue damage with limited superficial entry and exit wounds. Muscle necrosis can precipitate renal failure. Cardiac function should be assessed fully.

Chemical and radiation burns require decontamination and the input of a specialist burns team.

Chapter 2

Allergy

Host defence mechanisms

Innate immunity

- First line of host defence.
- Immediately active.
- **Non-specific**.

Mechanisms

- **Physical:** epithelial cells.
- **Chemical:** gastric acid, defensins (small proteins which act mainly by penetrating microbial cell wall and forming pores).
- **Immune:**
  - Soluble: acute-phase reactants, complement, cytokines.
  - Cellular: phagocytes—neutrophils, macrophages, eosinophils, mast cells, basophils, NK (natural killer) cells (Fig. 2.1).

Acute-phase reactants

- CRP.
- Serum amyloid P protein.
- Mannose-binding lectin.

Complement

- Series of plasma proteins.
- Nine basic complement components.
- Activators: classical, alternative, and lectin pathways (Fig. 2.2).
- Activates C3, a key component required to switch on the effectors.
- Effectors: anaphylatoxins, complement receptors, and membrane attack complex.
- Main effects:
  - Opsonization.
  - Chemotaxis and inflammation.
  - B-cell stimulation.
  - Immune complex clearance.
  - Cell lysis.
- Complement regulators: C1 inhibitor, C4 binding protein, complement receptor 1 (CR1), decay accelerating factor (DAF), factor H, factor I, and cluster of differentiation 59 (CD59).

Cytokines

- Small soluble intercellular messengers.

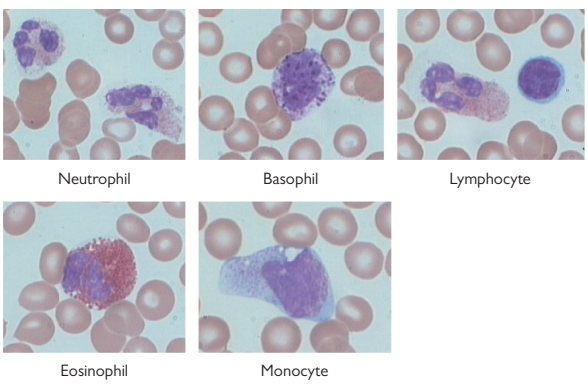


Fig. 2.1 Cells involved in host defence.
With permission from Dr Donald J. Innes, Jr., M.D.

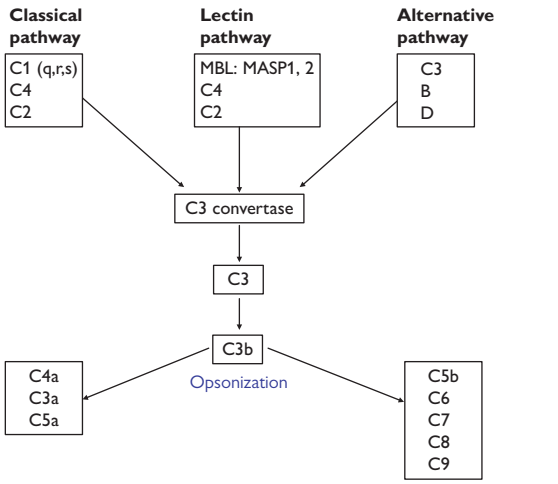


Fig. 2.2 The complement pathways.
The classical, lectin, and alternate pathways of complement activation. MBL: mannose-binding lectin; MASP: mannose-binding lectin-associated serine protease.

Interferons (IFNs)

- Type I—alpha and beta:
  - Produced by fibroblasts, monocytes, and virus-infected cells.
  - Antiviral, anti-proliferative.
- Type II—gamma:
  - Produced by activated T cells and NK cells.
  - Activate macrophage/neutrophil killing.
  - Stimulate NK cells.
  - Increase MCH class II expression.

Interleukins (ILs)

- IL-6, IL-8 (chemoattractant).

Chemokines

- Chemoattractant cytokines.

Neutrophils

- The principal phagocytic cells in the body.
- Without neutrophils survival is not possible.
- Released from bone marrow into the bloodstream in response to infection.
- Important role in phagocytosis and destruction of extracellular bacteria and some fungi.
- Surface receptors for immunoglobulin (Ig)-G, IgA, and complement components.

Eosinophils

- Important in parasite control and allergy.
- Produces: major basic protein, eosinophil cationic protein.
- Surface receptors for IgG, C3, and C5.

Basophils and mast cells

- Basophils circulate in blood, mast cells are tissue bound.
- Surface receptors for C3, C5, and IgE.

- Produce: histamine, prostaglandins, leukotrienes, platelet-activating factor, cytokines.
- Involved in the immune response to parasites.
- Interaction of antigen with bound IgE produces immediate hypersensitivity.

Natural killer cells

- Large granular lymphocytes.
- Kill cells bearing viral or tumour surface markers.

Pathogen recognition

- Pattern recognition receptors on immune cells recognize pathogen-associated molecular patterns (PAMPs) on micro-organisms.
- PAMPs: bacterial lipopolysaccharides (LPS), dsRNA, CpG, peptidoglycan.
- The main group of receptors for PAMPs are called Toll receptors.

Cell adhesion and recruitment

- Adhesion molecules: selectins, integrins, cadherins, intercellular adhesion molecules.
- Chemoattractants: chemokines, leukotriene B4, FMLP.

Phagocytosis and intracellular killing

- Pseudopodia spread around the organism or particle to form a phagosome.
- Phagolysosome: phagosome fuses with cytoplasmic granules. This exposes the microbe to the action of bactericidal components contained within lysosomes.
- Opsonization (coating of bacteria with specific antibody and complement) increases efficiency of phagocytosis.

Killing mechanisms operating within phagocytes

- Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-*dependent* mechanisms: depend on the generation of reactive oxygen molecules.
- NADPH oxidase-*independent* mechanisms act via proteolytic enzymes contained within lysosomes, e.g. cathepsin and elastase.

Adaptive immunity

- **Specific**.
- Depends on generation of specific antibodies and antigen-specific effector T cells.
- Takes time to develop.
- Characterized by development of immunological memory (generation of a pool of memory T and B cells).
- Hallmark of immune systems of higher animals.

CD molecules

- CD3: present on all T-cells; accessory molecule required for signalling via T-cell receptor.
- CD4: present on T-helper cells and monocytes; interacts with MHC class II antigens on antigen-presenting cells.
- CD8: present on cytotoxic T-cells, recognizes MHC class I antigens on target cells.

T lymphocytes

- 70–80% of total lymphocyte population (Fig. 2.3).
- Important role in intracellular infections, tumour surveillance, and graft rejection.
- Precursors formed in the bone marrow, undergo maturation in the thymus.

CD4+ T cells

- Helper T cells (Th).
- 60% of circulating T-cell population.
- Recognizes antigen when presented with class II MHC antigens.
- Provides help for B cells.

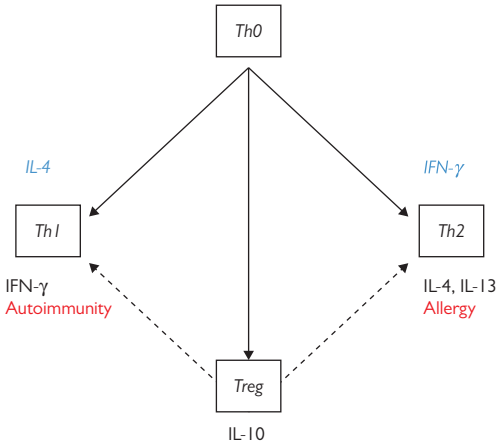


Fig. 2.3 CD4+ T-cell subsets. Subsets of CD4+ T cells and the prototype cytokines they produce. Treg: regulatory T cell; broken line refers to suppression of effect.

- Involved in type IV hypersensitivity.
- Th0 cells—naïve mature T cells which can differentiate into either Th1 or Th2 cells upon activation.

Th1-type CD4+ T cells

- When activated secrete IL-2 and IFN-γ.
- Are suppressed by IL-10.
- Produce cell-mediated immunity and type IV hypersensitivity reactions.

Th2-type CD4+ T cells

- When activated secrete IL-4, IL-5, IL-6, and IL-10.
- Are suppressed by IFN-γ.
- Cause B-lymphocyte proliferation and differentiation.
- Stimulate secretion of IgG, IgA, or IgE.
- Contribute to generation of antibody-mediated hypersensitivity reactions.

CD8+ T cells

- Cytotoxic T cells.
- 40% of circulating T-cell population.
- Recognize antigen presented by MHC class I antigens.
- Important in eliminating cells infected by viruses.

B lymphocytes

- Produced in the bone marrow, final maturation occurs in the spleen and lymph nodes.
- Express Igs on their cell surface.
- Differentiate into plasma cells; plasma cells secrete antibody.
- Activation of B cells by protein antigens needs both antigen and helper CD4+ T cells.
- Polysaccharides can produce B-cell activation without T-cell help.

Hypersensitivity reactions

What is hypersensitivity?

- Immune responses with excessive or undesirable consequences (Table 2.1).
- Can cause tissue or organ damage.

Type I: anaphylactic or immediate

- These reactions are initiated by antigen binding to antigen-specific IgE located on the surface of mast cells and basophils (Fig. 2.4).
- Cross-linking of mast cell-bound IgE molecules by antigen results in the activation of a signal cascade. This leads to the release of

Table 2.1 Details of the four different types of hypersensitivity reaction				
	Type I Anaphylactic/ immediate	Type II Antibody-dependent cytotoxicity	Type III Immune complex mediated	Type IV Cell mediated or delayed type
Onset	Seconds	Seconds	Hours	2–3 days
Effectors	IgE Mast cells Eosinophils	IgG Complement Phagocytes	IgG Complement Neutrophils	T cells (CD4+) Macrophages
Clinical examples	Anaphylaxis Hay fever Asthma	Transfusion reactions Goodpasture syndrome	SLE EAA (extrinsic allergic alveolitis)	Contact dermatitis

preformed mediators stored within secretory granules contained within mast cells (e.g. histamine, eosinophil cationic protein) as well as newly synthesized mediators derived from membrane phospholipids (**leukotrienes**).

- Reactions usually start within 30 minutes of antigen exposure.
- **Clinical significance:** type 1 hypersensitivity is responsible for anaphylaxis and also contributes to the pathogenesis of asthma and hay fever.

Type II: antibody-dependent cytotoxicity

- Initiated by binding of circulating IgM or IgG antibody to antigen located on cells or basement membranes.
- Tissue breakdown is due to complement activation and by activation of phagocytes attracted to the site by complement breakdown products (C5a).
- **Clinical significance:** type II hypersensitivity is responsible for Goodpasture syndrome, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, pemphigus, and pemphigoid (this is not an exhaustive list).

Type III: immune complex-mediated or Arthus reaction

- This is initiated by circulating antigen–antibody complexes which get deposited on endothelial surfaces of affected organs.
- Tissue damage is produced by complement activation and the attraction and activation of phagocytes by the immune complexes.
- **Clinical significance:** multi-organ damage in SLE is initiated by deposition of immune complexes of nuclear antigens and antinuclear antibodies. Immune complex deposition initiates pathology in extrinsic allergic alveolitis, allergic bronchopulmonary aspergillosis, and many forms of glomerulonephritis.

Type IV: cell-mediated or delayed type hypersensitivity

- This is produced by the activation of CD4+ T cells by antigen presented by antigen-presenting cells. The activated T cells

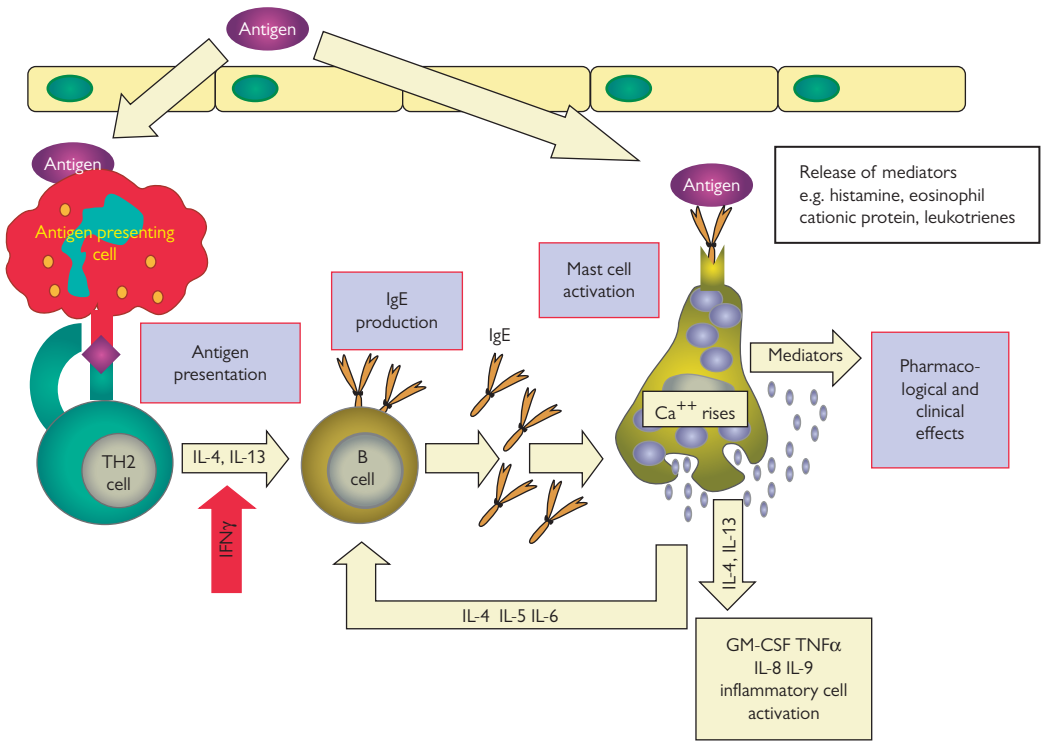


Fig. 2.4 Diagrammatic representation of events during a type 1 hypersensitivity reaction. Reproduced with permission of Dr. Richard Hunt, University of South Carolina.

produce cytokines which attract and activate monocytes producing granulomatous inflammation.

- Takes 48–72 hours to develop following antigen exposure; hence called delayed hypersensitivity.
- **Clinical significance:** this type of hypersensitivity is responsible for contact dermatitis, tuberculin reaction, tissue damage in mycobacterial disease. Sarcoid and Crohn disease are examples of granulomatous inflammation where the initiating antigen is unknown.

Autoimmunity

What is autoimmunity?

- State when antibodies and T cells recognize normal components of the body.

Autoimmune disease

- Occurs when the immune system fails to recognize the body's own tissues as 'self' and attacks itself.
- Mediated by type II, III, and IV hypersensitivity reactions.
- Tends to run in families.
- There is often a female preponderance.
- Individuals with one autoimmune disease are more likely to develop another.

Mechanisms of autoimmunity

Immunological tolerance

- During T-cell development in the thymus, self-reactive T cells are identified and undergo apoptosis or programmed cell death.
- Autoimmune B cells are generally deleted or rendered unresponsive during development in the bone marrow.
- Any autoreactive lymphocytes that reach the periphery are held in check by the action of a population of CD4+CD25+ T cells called T-regulatory cells.
- Autoimmunity arises when immunological tolerance breaks down.

Breakdown of thymic tolerance

- Inheritance of a human leucocyte antigen (HLA) allele that does not bind self-antigen. Autoreactive T cells are not deleted.
- Inheritance of gene polymorphisms that reduces thymic expression of normal peptide antigens. T cells that recognize these peptide antigens are not deleted.
- Release of sequestered/cryptic antigens to which the immune system is not tolerant. Examples of such antigens are ocular antigens.

Breakdown of peripheral tolerance

- Activation of the immune system by microbial PAMPs may reverse autoreactive T-cell anergy. This may occur during microbial infections.
- Cross reactivity and molecular mimicry between microbial antigens and self antigens of the host may lead to a breakdown of self-tolerance. Initiation of cardiac damage following infection with *Streptococcus pyogenes* as occurs in rheumatic fever is an example of this mechanism.
- Failure of T-suppressor cell function has been postulated to produce autoimmunity.

2.2 Atopy

Definition

- Genetic susceptibility to allergy—manifestations: allergic rhinitis, atopic eczema, allergic asthma.

Genetic susceptibility

- If one parent is atopic, a child has 25–40% chance of being atopic.
- Both parents atopic: risk rises to 70–80%.
- HLA associations with atopy: HLA-A1, -B8, -DR3, -A3.
- Other gene associations: IL-4, IL-5, IL-13, high-affinity IgE receptor β-subunit, IL-4 receptor α-subunit, ADAM33 metalloproteinase.

Mechanisms of allergy

- Allergen-specific IgE binds high-affinity FcεR1 receptors on mast cells.
- On subsequent allergen exposure, surface IgE molecules are cross-linked initiating a cascade of intravascular events.
- Mast cells degranulate liberating preformed mediators (Fig. 2.5).
- Synthesis and release of newly-formed mediators including leukotrienes.
- Action of mediators results in:
  - Increased vascular permeability (swelling).
  - Increased airway reactivity (bronchoconstriction).
  - Increased mucosal secretion contributing to airway narrowing.
  - Dilatation of post-capillary venules leading to reduced venous return and secondary hypotension during severe reactions.

History

- Most important aspect for making the correct diagnosis.
- Tests are ordered based on the history.

Skin prick testing (SPT)

- Used to detect *in vivo* antigen-specific IgE antibodies.
- Done by pricking skin through a drop of diluted antigen placed on the skin; positive reaction produces a wheal >3mm in diameter (or 2mm more than negative control).
- Advantages: rapid, relatively cheap, more clinically informative (*in vivo* test) (Fig. 2.6).
- Disadvantages: limited availability of standardized reagents, anaphylaxis (very rare), trained staff needed to interpret test.

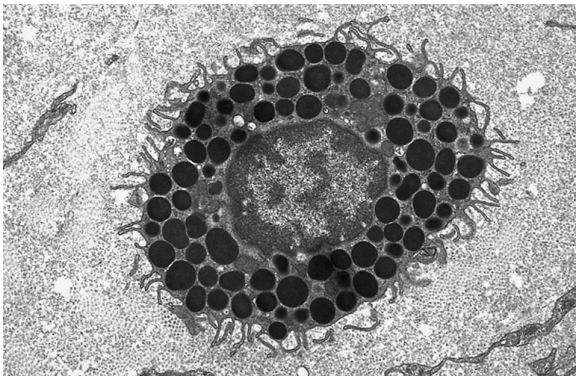


Fig. 2.5 Mast cell containing multiple granules.

Reproduced from Vaughan DW, *A Learning System in Histology: CD-ROM and Guide*, 2002, by permission of Oxford University Press, USA, www.oup.com

Drugs such as anti-histamines/steroids/calcium channel blockers/antidepressants may interfere with the test.

Measurement of specific IgE in blood: radioallergosorbent test (RAST)

- Semi-quantitative, six grades (0–6) or fully quantitative (expressed as kUA/L (kilounits of allergen per litre)).
- Levels usually do not correlate with severity of clinical disease.
- Preferred in the following settings:
  - Severe and extensive eczema.
  - Very young child.
  - Patients being treated with antihistamines.
  - Patients with significant risk of anaphylaxis.

Total IgE

- Not always raised in allergic individuals with elevated antigen-specific IgE antibody levels.
- Levels can be significantly raised in: parasitic infections, atopic dermatitis, hyper IgE syndrome (typically >2000IU/L).
- Of little value in the assessment of patients with suspected allergy.

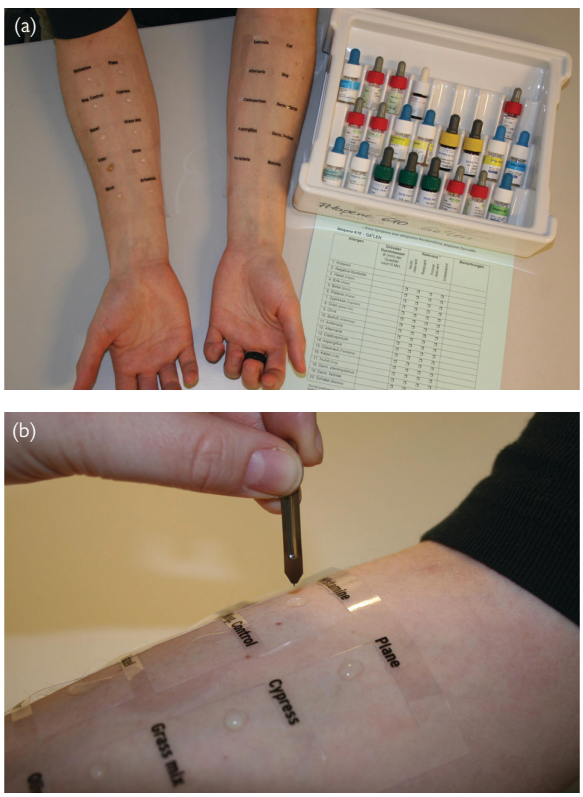


Fig. 2.6 (a) Preparation for skin prick test on forearm. (b) Prick testing with lancet through a drop of allergen extract.

Reproduced from Heinzerling et al., 'The skin prick test: European Standards', *Clinical and Translational Allergy*, 3, 3, February 2013, © 2013 Heinzerling et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Challenge tests

- Open challenge by administering suspected allergen with resuscitation measures to hand; should only be done by an experienced physician.
- Double-blind placebo controlled challenge: is the gold standard but rarely used in practice.

Allergic rhinitis

- **Seasonal** symptoms due to allergy to pollen/moulds.
- **Perennial** (year-round) symptoms due to allergy to house dust mite (HDM), cat or dog.
- History:
  - Red, itchy, runny nose.
  - Itchy, swollen watery eyes.
- Investigation:
  - Skin prick test.
  - Measurement of allergen-specific IgE.
- Management:
  - Allergen avoidance: pets, HDM.
  - Pharmacological.
  - Non-sedating antihistamines.
  - Nasal corticosteroids (use regularly for at least 2–3 weeks for noticeable benefit).
  - Allergen desensitization: good evidence for the efficacy of desensitization to a number of antigens including grass.

2.3 Food, drug, latex, and venom allergy

Food allergy

- A group of disorders caused by an immune response to proteins in food.
- Need to distinguish between IgE-mediated food allergy and food intolerance (due to non-immunological and psychogenic causes).
- Most reactions are caused by a limited number of foods:
  - In children: milk, egg, peanuts, tree nuts, wheat, and soy.
  - In adults: peanuts, tree nuts, fish, and shellfish.

IgE-mediated food allergy

- Common in children—0.5% allergic to cows' milk.
- Most food allergens: heat stable (resist cooking), acid stable (resist stomach acid).
- Signs and symptoms occur within minutes to a couple of hours of food consumption.
- May cause local symptoms affecting the gastrointestinal tract, skin, and respiratory tract. Can rarely cause systemic life-threatening reactions.
- Diagnosis is based on history of reactions occurring on exposure; sensitivity is confirmed by skin tests or RAST tests.

Cows' milk allergy

- Common (especially among children).
- Usually disappears by the age of 5 years.
- Major milk allergens: β-lactoglobulin, α-lactalbumin, casein, bovine serum albumin, and bovine Igs.

Egg allergy

- Common in children <5 years; also relevant for adults.
- Often disappears with age.
- Major egg allergens: ovomucoid and ovalbumin.
- Anaphylactic responses may occur.

Fish and shellfish allergy

- Shellfish: crustacea (prawns, crabs, and lobsters); molluscs (mussels, scallops, and oysters).
- May be severe.
- Usually permanent.

Peanut allergy

- Major cause of severe allergic reactions.
- May not be declared on labels.
- Avoidance may be difficult.
- Sensitization may occur through the use of groundnut oil in formula milks and emollient creams.
- Most cases start during infancy and can be long-lasting.
- Most affected individuals are atopic.

Tree nut allergy

- Walnut, almond, brazil, and hazel nuts are the most common causes but reactions to all types of tree nuts are documented.
- Can give rise to anaphylaxis.

Cereal allergy

- Wheat, barley, and rye are closely related.
- Can cause: IgE-mediated allergic response, gluten intolerance (coeliac disease), or occupational asthma.
- Rice and maize allergies are rare.

Oral allergy syndrome

- Pollen-allergic individuals may develop allergic reactions to soft fruits (plum, peach, apples) or vegetables due to the presence of antigenically similar proteins in the fruit or vegetable.
- Heat-labile allergens—allergy is produced by *raw* fruit but not cooked or canned fruit.
- Fresh extract of suspected food required for skin testing.
- Reported cross reactivities:
  - Birch pollen: hazelnut, almonds, apple, peach, pear, plums, cherries, carrot.
  - Grass pollen: melon, tomato.
  - Ragweed pollen: melon, banana.

Food intolerance

- Pharmacological: tyramine (headaches, hypertension in patients on monoamine oxidase inhibitors (MAOIs)), caffeine, alcohol.
- Enzyme deficiencies: lactase deficiency (common in Asian people).
- Toxic: scombotoxin (spoiled mackerel/tuna), *Bacillus cereus* food poisoning, monosodium glutamate (Chinese restaurant syndrome).
- Bowel disorders: irritable bowel syndrome, coeliac disease, Crohn disease, infections (*Giardia, Yersinia*).
- Pancreatic insufficiency: cystic fibrosis.
- Psychogenic.

Drug allergy

Allergic reactions to drugs represent 5–10% of all adverse reactions to drugs.

Mechanisms of drug allergic reactions include:

- Hypersensitivity: types I, II, III, or IV.
- Direct histamine release (opiates, radiocontrast media).
- Undue sensitivity to the pharmacological effect (NSAIDs).
- Direct complement activation.

Penicillin allergy

- Common.
- Severe reactions are rare.
- Major antigenic determinants—benzylpenicilloyl nucleus.
- Minor antigenic determinants—benzylpenicillin, benzyl penicilloate, and others.
- Both capable of causing severe immediate reactions.

Clinical manifestations

- Anaphylaxis (type I).
- Haemolytic anaemia (type II).
- Serum sickness (type III).
- Interstitial nephritis, contact dermatitis (type IV).
- Stevens–Johnson syndrome (unknown mechanism).

Investigation

- RAST and SPT/intradermal testing (IDT):
  - Detects type I hypersensitivity.
  - Not predictive of other types of reactions.

There are no reliable laboratory tests that can detect other types of hypersensitivity reactions to penicillin or other drugs.

Difficulties with obtaining skin test reagents containing minor determinants.

- Up to 5% of SPT positive penicillin-allergic patients may react to cephalosporins.
- High level of cross-reactivity with carbapenems and the monobactams (β-lactam ring semisynthetic penicillins).
- IgE can be directed at shared side-chain (aztreonam and ceftazidime).

Management

- Avoid penicillin and other semi-synthetic β-lactam antibiotics.
- Desensitization for patients with IgE-mediated allergy if penicillin is essential:
  - No lasting tolerance.
  - Not to be attempted if patient had a Stevens–Johnson reaction.

Insulin allergy

- The tertiary structure of human insulin is changed during manufacturing process.
- Protamine and zinc may cause reactions.

Manifestations

- Urticaria/induration at the injection site.
- Systemic reactions (rare).

Treatment

- Difficult.
- Local reaction: antihistamines, hydrocortisone with the insulin.
- Try using a different insulin preparation.
- Desensitization.

Anaesthetic allergy

- Royal College of Anaesthesia guidelines available.
- Mechanisms: IgE-mediated, direct mast cell degranulation (opioids), complement activation (solvents).

Causes

- Muscle relaxants (suxamethonium, rocuronium).
- Latex.
- Antibiotics.
- Plasma expanders/blood products.
- Less commonly reactions may occur to other anaesthetic agents.

Management

- Mast cell tryptase: at time of reaction, 3 and 24 hours later.
- Refer to a specialist centre for investigation with a copy of drug chart and observation chart kept during the anaesthetic procedure.
- Most patients will need skin tests with diluted drugs to identify the agent responsible for the allergic reaction; this should only be done by experienced investigators.
- RAST tests currently limited to suxamethonium and thiopentone.

Latex allergy

- Increasing problem in hospitals: 20% of staff in theatres or ITU may become sensitized.

Presentation

- Type I reactions:
  - Anaphylaxis, asthma, angio-oedema, rhinoconjunctivitis, contact urticaria.
- Materials: gloves, condoms, clothing, bungs of drug vials.
- Food cross-reactivity: bananas, avocado, kiwi fruit, potato, tomato, chestnut, lettuce, pineapple, papaya.
- Type IV reactions:
  - Contact hypersensitivity to additives used in processing rubber.

Diagnosis

- Type I reactions:
  - Based on history and confirmation of latex sensitization.
  - RAST: 60–80% sensitive.
  - SPT: 95% sensitive.
  - Use standardized commercial latex reagents for skin test.
- Type IV reactions:
  - Identified by patch testing.

Management

- Type I reactions:
  - Avoidance of contact with rubber-containing articles essential (Table 2.2).
  - Education of patient, healthcare professionals, and employers is essential; provide written information.
  - Occupational issues can be difficult.
  - Hospitals and dental surgeries: latex-free equipment must be available in key areas (theatres, A&E, Medical Admissions).
- Hospital trusts need latex policy (Health and Safety Executive requirement).
- Latex allergy support group: information on latex content of products (<www.lasg.org.uk>).
- Pharmacy: advice on latex content of drugs.

Insect venom allergy

- Bee or wasp venom.
- High risk: bee keepers, forestry workers.
- Reactions can be: minor/limited or major/systemic (potentially fatal).

Treatment

- Depends on severity of previous reaction, risk of future stings.
- Emergency kit: antihistamines, injectable adrenaline.
- Desensitization: vaccines made from venom induce long-term tolerance to the allergen; refer for specialist advice.

Table 2.2 List of products containing latex

Dipped products
Gloves
Balloons
Tourniquets
Catheters
Condoms
Dry rubber
Tyres
Syringe plungers
Vial stoppers
Shoe soles

2.4 Urticaria and angio-oedema

Urticaria

This term is used to describe an elevated papular or plaque-like eruption that is intensely pruritic; each lesion lasts for <24 hours.

- Affects 10–20% of individuals at some time.
- Swelling involves superficial dermis.
- May occur alone or with angio-oedema (swelling involving the deeper dermis and subcutaneous tissue).
- Acute urticaria: symptoms of short duration.
- Chronic urticaria: symptoms lasting >6 weeks.

Acute urticaria

- Cause usually obvious from history and include:
  - Food.
  - Drugs.
  - Contact with allergies (e.g. latex, plants, foods).
  - Viral infections.
  - Parasitic infections.
  - Insect bites.

Physical urticarias (~10%)

- Cold: induced by exposure to cold; rare familial form due to mutation of cryopyrin gene; acquired form due to cryoglobulins or infections.
- Cholinergic: induced by exercise or heat.
- Pressure: produced by physical pressure on skin.
- Vibration: induced by vibration in contact with skin.
- Solar: produced by sun exposure; exclude porphyria.

Chronic urticaria

- Cause is not evident in >90% patients (Fig. 2.7).
- Autoantibodies to FcεR1 and IgE are found in serum of 30–40% of patients.
- ~5–10% of patients have associated autoimmune thyroid disease (treatment of thyroid disease does not, however, cure urticaria).

Special categories of urticaria

- Urticaria pigmentosa: cutaneous manifestation of systemic mastocytosis.

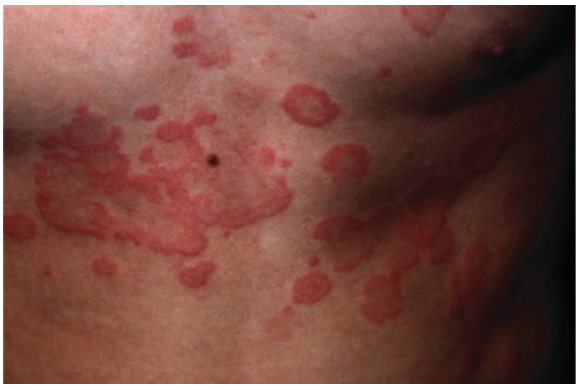


Fig. 2.7 Widespread ordinary urticaria. The smooth erythematous papules and plaques may expand into annular shapes.

Reproduced from Burge S. and Wallis D., *Oxford Handbook of Medical Dermatology*, 2010, Figure 11.1, page 215, with permission from Oxford University Press.

Urticarial vasculitis

- Lesions persist >24 hours.
- Brown stain left when lesions fade.
- Biopsy: leucocytoclastic vasculitis.
- Associated with reduced serum C3, C4, and C1q levels.
- Various aetiologies including SLE and auto-antibodies to C1q.

Pathogenesis

- Mast cell activation with local release of mediators.
- Activation of the complement and kinin pathways.
- Autoantibodies against IgE and the IgE receptor (FcεR1).
- Perivascular leucocytic infiltrates.

Diagnosis

- History is very important.
- Look for dermatographism, appearance of lesions.
- Physical causes: pressure tests, ice cube test.
- Allergy testing: usually of no value in chronic urticaria.
- Laboratory investigations are not usually helpful.
- In chronic urticaria check thyroid function and FBC.
- Cold urticaria: check for family history, check for cryoglobulins.
- Autoantibodies useful in cases of suspected urticarial vasculitis (ANA, extractable nuclear antigen (ENA), dsDNA, rheumatoid factor (RF)).
- Complement studies indicated in suspected urticarial vasculitis: C3, C4, C1q level.
- Skin biopsy: if urticarial vasculitis suspected.

Treatment

- Acute urticaria readily responds to antihistamines.
- Chronic urticaria may last up to 2–3 years before going into remission.
- First-line treatment comprises non-sedative, long-acting antihistamines (e.g. cetirizine, levocetirizine, fexofenadine, loratadine).
- May need higher than average dose.
- Prescribe daily treatment for 3 months and then try to withdraw therapy.
- If non-sedative antihistamines alone are not effective, add sedative antihistamine (e.g. hydroxyzine).
- Some patients not responding to H1 receptor antagonists alone respond to addition of H2 receptor blockers or leukotriene antagonists.
- Third-line treatment in patients not responding to above: omalizumab, ciclosporin, sulphasalazine. In these circumstances refer to specialist centre.

Angio-oedema

Deep tissue swelling. May occur alone or be associated with urticaria.

Epidemiology

- Idiopathic: 15% of general population.
- Sex: ♂>♀.

Aetiology

- Allergic.
- Physical (pressure, vibration, cold).
- Drugs (ACE inhibitors, NSAIDs, statins, proton-pump inhibitors (PPIs)).

- Hereditary C1 inhibitor deficiency.
- Acquired C1 inhibitor deficiency: SLE, lymphoma.
- Idiopathic: diagnosis made when other causes excluded; this is the **most common** condition.

Pathogenesis

- Fluid leaks from post-capillary venules.
- Activation of the kinin system with bradykinin production.
- ACE inhibitors inhibit bradykinin breakdown.
- C1 inhibitor protein has a role in complement and clotting systems. It is also a control protein for the kinin cascade.

Clinical presentation

- Rarely itchy.
- Tends to give discomfort from pressure.
- Premonitory tingling before the swelling occurs in C1 inhibitor deficiency.
- Severe abdominal pain due to angio-oedema of intestinal tissue; these attacks may mimic an acute abdomen.

History

- Accompanied by urticaria or anaphylaxis (allergic).
- Association with:
  - Physical stimuli.
  - Drug exposure.
- Family history (hereditary C1 inhibitor deficiency).
- Connective tissue disease.
- Lymphoma (may be occult).
- Angio-oedema **with** urticaria will not be due to hereditary angio-oedema.
- Angio-oedema **without** urticaria: exclude C1 esterase inhibitor deficiency.

Diagnosis

Allergen-specific IgE: skin prick tests or RAST tests.
C1 inhibitor deficiency:

- C4 will be low (even between attacks).
- C1 inhibitor level is reduced in 85% of patients.
- C1 inhibitor function is very low/absent in 100% of cases.

If acquired C1 inhibitor deficiency is suspected: check for a paraprotein in serum and seek advice from an immunologist regarding further investigation.

Management

Treatment is dependent on the cause:

- Avoid trigger: allergen, NSAIDs, ACE inhibitors.
- Antihistamines comprise the mainstay of treatment.
- Short courses of steroids are indicated for severe attacks.
- Airway compromise is very uncommon except in C1 inhibitor deficiency and ACE-inhibitor induced angio-oedema.

Hereditary C1 inhibitor deficiency

- Prevention of angio-oedema achieved by use of modified **androgens** (stanozolol 2.5–10mg/day; danazol 200–800mg/day). Monitor LFTs every 4–6 months and consider annual ultrasound scan of liver.
- **Antifibrinolytics** (tranexamic acid 2–4g/day) can prevent attacks but may be less effective. Main indication is to treat symptomatic children before linear growth is complete.
- **Purified C1 inhibitor** is the treatment of choice for angio-oedema with risk of respiratory obstruction or in patients with severe abdominal pain. An alternative is **fresh frozen plasma**.
- **Icatibant (Firazyr®)**: synthetic oligopeptide, Bradykinin receptor antagonist, blocks bradykinin type 2 receptor, approved in the EU for treatment of acute attacks, subcutaneous injection (pre-filled syringe).
- Major surgery or dental extraction should be covered by prophylactic infusions of C1 inhibitor concentrate.
- This is an autosomal dominant trait, therefore genetic counselling and family studies are important.

Acquired C1 inhibitor deficiency

- Improved by effective treatment of the underlying disease.
- Treatment is difficult; seek specialist advice.

Complications/prognosis

- Sudden death may occur due to laryngeal oedema in C1 inhibitor deficiency. Before androgenic steroids were used for prophylaxis, the condition had high mortality due to respiratory obstruction.
- Respiratory obstruction can also occur in ACE-inhibitor induced angio-oedema but is very rare in **idiopathic** angio-oedema.
- Recurrent abdominal pain (GI involvement) can occur in C1 inhibitor deficiency; it may be mistaken for an acute abdomen and lead to exploratory laparotomy.
- Increased incidence of SLE in C1 inhibitor deficiency.

Prevention

- Patients with a history of angio-oedema for any reason should **never** be given ACE inhibitors or oestrogen-containing contraceptive agents. These drugs may precipitate life-threatening angio-oedema.

2.5 Anaphylaxis

Definition

- Severe systemic allergic reaction involving respiratory difficulty and/or hypotension.

Incidence

- 1:2300 attendees at emergency departments (EDs).
- Incidence at hospital discharge with a primary diagnosis of anaphylaxis:
  - 5.6/100,000 (1991/92).
  - 10.2/100,000 (1994/95).
- 214 deaths attributed to anaphylaxis in the UK between 1992 and 2001.

Mechanism

- Anaphylactic reactions are IgE-mediated.
- Similar reactions which are non-IgE mediated are called **anaphylactoid** reactions.
- The sequence of events is as follows:
  - Production of IgE in susceptible individual (sensitization).
  - IgE sensitized mast cells and basophils.
  - Exposure to allergen leads to mast cell degranulation and release of chemical mediators including histamine, leukotrienes, and platelet activating factor.
- Mediators act on blood vessels to cause leakage of fluid from the circulation and also cause vasodilatation which further reduces venous return to the heart.
- Mediators also cause bronchoconstriction.

Causes

- Foods: peanuts, tree nuts (e.g. almonds, walnuts), fish, shrimps, shellfish, egg, milk, sesame, gelatin.
- Drugs.
- Latex.
- Insect venom.
- Radiocontrast media (mainly anaphylactoid reactions).
- Vaccinations.
- Biological fluids (e.g. seminal fluid and biological therapeutic agents).
- Anaesthetic agents and muscle relaxants.
- Exercise (rare).
- Idiopathic (rare).

Clinical manifestations

- Erythema.
- Pruritus—generalized.
- Urticaria, angio-oedema.
- Laryngeal oedema.
- Difficulty in swallowing or speaking.
- Rhinitis.
- Conjunctivitis.
- Severe asthma/tightness of the chest.
- Nausea, vomiting, abdominal pain, diarrhoea.
- Sense of impending doom.
- Palpitations.
- Fainting, dizziness.
- Collapse, loss of consciousness.

All these features may not be evident in all cases.

Diagnosis

- Based on clinical grounds and should be made in the presence of hypotension and/or respiratory compromise together with any of the other features listed under 'Clinical manifestations'.
- Obtain any records from acute event.
- Detailed history including suspected inducing agent, route, dose, sequence of symptoms, treatment, associated factors (exercise, medications).

Differential diagnosis

- Vasovagal syncope.
- Syndromes associated with flushing (e.g. carcinoid).
- Angio-oedema secondary to ACE inhibition.
- Panic attacks.
- Scromboid poisoning.

Laboratory confirmation

- Serum mast cell **tryptase** (not elevated in all cases).
- Collect serial blood samples at 30-minute intervals for 2 hours ideally (or a single sample with a later baseline).
- Allergen-specific IgE (SPT, RAST): useful to confirm antigen specificity but not to be performed at the time of an active episode.

Treatment

Immediate

ABC approach (see Section 1.1 and Fig. 2.8):

- Maintain airway, administer oxygen, treat hypotension (IV fluids, vasopressors).
- Adrenaline: 0.5mg 1:1000 solution IM (not IV unless cardiac monitoring available and drug highly diluted).
- Chlorpheniramine IV.
- Hydrocortisone IV (for preventing late phase effects).
- Treat bronchospasm.
- Once recovered observe for 24 hours for possible late-phase relapse.

Long term

- Identify and train patient to avoid responsible agent (specialist referral is ideal).
- Teach patient/carers how to identify and treat anaphylactic reaction.
- Issue pre-loaded adrenaline injection kits and training in their use: EpiPen®, Anapen®.
- Doses: adult (300mcg, more may be needed in a large adult), child (150mcg).
- Recommend a MedicAlert bracelet.
- Patient information from The Anaphylaxis Campaign (<http://www.anaphylaxis.org.uk>).

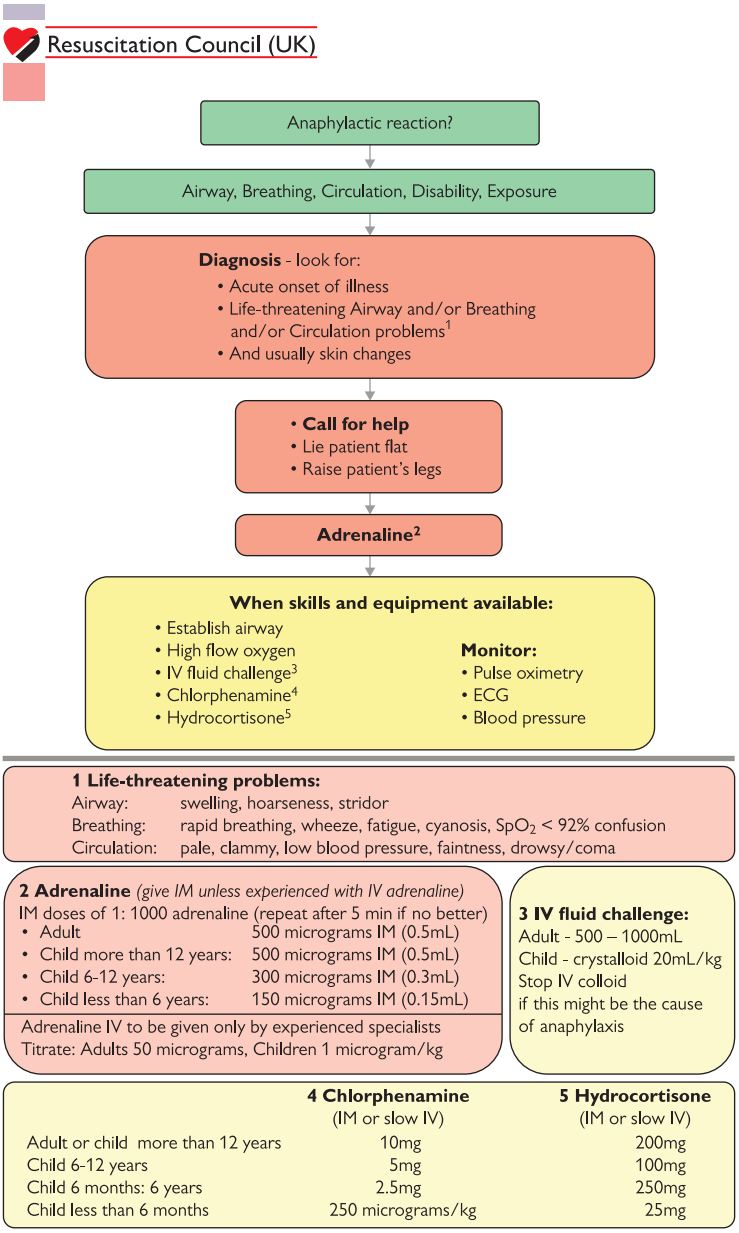


Fig. 2.8 Resuscitation treatment algorithm for first medical responders to anaphylactic reactions in adults.
IM: intramuscular; IV: intravenous.
Reproduced with the kind permission of the Resuscitation Council (UK).

2.6 Approach to the immunosuppressed individual

Warning signs of immunodeficiency

- Failure to thrive during infancy.
- Eight or more new infections in a year.
- Two or more serious sinus infections in a year.
- Two or more episodes of pneumonia in a year.
- Recurrent deep skin or organ abscesses.
- Two or more deep-seated infections (osteomyelitis, liver abscess).
- Persistent oral or cutaneous thrush >1 year old.
- Antibiotics for 2 months without effect.
- Surgical intervention for chronic infection (e.g. lobectomy, recurrent drainage of abscess).
- Family history of primary immunodeficiency.

Suspect underlying immunodeficiency if infections are:

- **S**erious: e.g. meningococcal septicaemia.
- **P**ersistent: e.g. oral candidiasis resistant to local therapy.
- **U**nusual: organism, e.g. *Aspergillus*, non-tuberculous mycobacteria (NTM), *Pneumocystis*.
- Site: e.g. liver or bone.
- **R**ecurrent:
  - Recurrent upper or lower respiratory tract infection.
  - Two major infections in 1 year.
  - One major and recurrent minor infections in 1 year.

Investigation for suspected immunodeficiency

History

- Infections (site, severity, need for antibiotics, hospital admissions).
- Failure to thrive.
- Surgical operations (grommets, lobectomies).
- Chronic diarrhoea: severe combined immunodeficiency (SCID), antibody deficiencies.
- Autoimmunity: common variable immunodeficiency (CVID), hyper-IgM syndrome.
- Immunization history.
- Childhood infections.
- Family history (consanguinity, unexplained sudden deaths).
- Risk factors for human immunodeficiency virus (HIV).
- Immunosuppressive therapy.

Examination

- Failure to thrive (weight/height).
- Ears, sinuses, lungs.
- Lymph node hyperplasia.
- Mouth ulceration: neutropaenia.
- Signs of autoimmunity: vitiligo, alopecia.
- Skin rash (atypical eczema): Wiskott–Aldrich syndrome, hyper-IgE syndrome, Omenn syndrome.
- Chronic osteomyelitis/deep seated abscesses: chronic granulomatous disease (CGD).
- Hepatosplenomegaly: CVID, Omenn syndrome.

Laboratory

Specialized investigations always required; seek advice of immunologist and infectious disease specialist first.

Microbiology

- Microscopy and culture as appropriate.
- Molecular techniques: PCR for microbes.
- In patients with immunodeficiency, serology is unreliable for diagnosis of infection.

Immunology

- The microbial pathogen and site of infection may be the first pointer to the probability and type of immune defect (Table 2.3).
- The more virulent the organism (e.g. measles), the less likely that there is an immune defect, whereas infections with organisms of low-grade virulence (e.g. *Pneumocystis*) should arouse suspicion.

Patients with disorders of the immune system tend to present in one of five ways, depending on the nature of the defect:

Presentation 1

- Recurrent, severe, unusual **pyogenic** infections, most commonly of the upper or lower **respiratory tract**, usually by encapsulated bacteria.
- Infants with failure to thrive (sometimes).

Investigate for **antibody** defect (sometimes complement deficiency): serum IgG, IgA and IgM levels.

Immunoglobulin levels vary with age. Antibody deficiency is present if levels are below the 5th centile confidence limits for age.

Presentation 2

- Recurrent **pyogenic skin** sepsis (cellulitis, abscesses) without explanation (i.e. eczema, excoriation) or visceral abscesses (lung, liver, lymph nodes), often caused by *Staphylococcus aureus*.
- Invasive fungal infection.
- Recurrent or persistent oral/mucocutaneous ulceration.
- Unexplained granulomatous inflammation.

Investigate for abnormality in **phagocytosis**:

- Absolute neutrophil count (may need repeating to exclude cyclical neutropaenia).
- Phagocyte oxidase function (to exclude CGD).
- Neutrophil and lymphocyte surface marker analysis to exclude leucocyte adhesin deficiency.

For serious/recurrent encapsulated bacterial sepsis exclude asplenia by splenic ultrasonography and blood film for red cell inclusions (Howell–Jolly bodies).

Table 2.3 Nature of organisms as a guide to the immunodeficiency state

Category of organism	Types of defect
Encapsulated bacteria, e.g. *S. pneumoniae*, Hib	Antibody Complement (rare) Asplenia (anatomical or functional) Innate immune deficiency
S. aureus Gram-negative bacteria Invasive fungal infection	Phagocytic Innate immune deficiency
Viral infections (especially reactivation of latent viruses e.g. CMV) Intracellular bacteria, e.g. mycobacteria Fungi, e.g. mucocutaneous candidiasis pneumocystis Protozoa, e.g. Toxoplasma, cryptosporidium	Cell-mediated immunity (caused by primary and secondary immunodeficiency; think of HIV) Innate immune deficiency

Presentation 3

- Failure to thrive from early **infancy**, especially if associated with intracellular pathogens (viruses—cytomegalovirus (CMV), *Herpes simplex*, bacteria—mycobacteria, fungi—*Candida, Pneumocystis*).
- Sometimes features of graft-versus-host reaction from materno-fetal or postnatal blood transfusions (skin rash, diarrhoea, hepatomegaly, lymphadenopathy) are observed.
- Infants with HIV may present in this way.

Investigate for defective **cell-mediated immunity**:

- Absolute lymphocyte count.
- Lymphocyte surface marker analysis to enumerate T, B, and NK cells.
- Lymphocyte function tests.

(Note: poor antibody production may also be a consequence of T-cell deficiency and patients may present with pyogenic bacterial infections.)

Presentation 4

Patients with infections caused by one or more of the following micro-organisms:

- Viruses (especially reactivation of latent viruses e.g. CMV), persistent *Molluscum contagiosum*, extensive human papilloma virus infection.
- Intracellular bacteria (*Mycobacterium tuberculosis* or disseminated NTM infection, *Listeria, Salmonella*).
- Fungi (mucocutaneous candidiasis or invasive aspergillosis, *Pneumocystis* pneumonia).
- Protozoa (*Toxoplasma, Cryptosporidium*).

Presentation 5

- Immunodeficient patients can present with *autoimmune* or *chronic inflammatory* diseases. It is thought that the basic abnormality leading to immunodeficiency may also lead to faulty discrimination between self and non-self, and thus to autoimmune disease.
- The manifestations of these disorders may be limited to a single target cell or organ (e.g. autoimmune haemolytic anaemia, thrombocytopenia, or thyroiditis), or may involve a number of different target organs (e.g. vasculitis, SLE or rheumatoid arthritis (RA)).
- The autoimmune and inflammatory diseases are more commonly seen in:
  - CVID.
  - Selective IgA deficiency.
  - Chronic mucocutaneous candidiasis.
  - Deficiencies of early components of the classical complement pathway (C1–C4).
- Occasionally a disorder that appears to be autoimmune in nature may, in fact, be due to an infectious agent. For example, the dermatomyositis that is sometimes seen in patients with X-linked agammaglobulinaemia is really a manifestation of chronic enterovirus infection and not an autoimmune disease.

2.7 Immunodeficiency

Definition

- Immune system unable to respond appropriately and effectively to infectious micro-organisms.

Causes of immunodeficiency

- **Primary immunodeficiency:**
  - Due to an intrinsic defect in a component of the immune system.
  - Usually due to a single gene defect and is therefore heritable.
- **Secondary immunodeficiency** (more common):
  - Drugs: corticosteroids.
  - Infection: HIV, Epstein–Barr virus (EBV).
  - Malignancy: lymphoproliferative disease.
  - Malnutrition.
  - Systemic disease: liver/renal failure, diabetes.
  - Splenectomy.

Primary antibody deficiency

X-linked agammaglobulinaemia (XLA)

- Mutation in Bruton tyrosine kinase, *BTK* gene (X chromosome).
- B-cell maturation arrest (pro-B to pre-B stages).
- Recurrent infections: sinus, pulmonary, ears.
- Main pathogens: *Streptococcus pneumoniae* and *Haemophilus influenza*.
- Recurrent infections lead to bronchiectasis and chronic sinus damage.
- Diarrhoea and malabsorption may occur (due to overgrowth of commensal bacteria in small intestine) or chronic infections with enteric pathogens.
- Meningoencephalitis: *Enterovirus*.
- Arthritis: *Ureaplasma*/*Mycoplasma*.

Diagnosis

- All immunoglobulins absent or low.
- B-cell lymphopenia with normal numbers of T and NK cells.
- A defect in the *BTK* gene or expression is confirmed (by DNA, mRNA, or protein analysis).

Management

- Ig replacement therapy by intravenous or subcutaneous route.
- Antibiotics.
- No live vaccines.
- Genetic counselling.

IgA deficiency

- **Most common UK primary immunodeficiency, 1:600**.
- IgA 0.05g/L.
- Majority are asymptomatic and healthy.
- A small proportion may be associated with an increased risk of sino-pulmonary infections; this is causally associated with poor specific antibody responses to bacterial capsular polysaccharides.
- Increased incidence of atopy, coeliac disease, and other autoimmune diseases.

Common variable immunodeficiency (CVID)

- Commonest *symptomatic* antibody deficiency.
- May present at any age.
- Peak age of presentation: early childhood/adulthood.
- Recurrent respiratory infections and gastrointestinal complications (as for X-linked antibody deficiency).
- ~1/5 develop autoimmune disorders (cytopenias, endocrinopathies, chronic hepatitis).
- Sarcoid-like systemic granulomatous disease can affect lungs, liver, and spleen.
- Lymphopenia: reduction of naïve T and B cells common.
- Complications: bronchiectasis/chronic sinus disease, malabsorption, increased risk of malignancy (lymphoma/gastric carcinoma).

Diagnosis

- Reduction of serum immunoglobulins below 5th centile for age.
- Associated with absent specific antibodies to routine childhood vaccines (if testing vaccine responses avoid live vaccines).

Management

- Immunoglobulins and antibiotics as for XLA.
- Systemic granulomatous disease may need steroids.

Specific antibody deficiency

- Clinical history suggestive of antibody deficiency.
- Total IgG and IgG subclasses normal.
- Pathogen-specific IgG levels and immunization responses deficient.
- Treat with appropriate immunizations, antibiotics, and immunoglobulin replacement.

IgG subclass deficiency

- Serum IgG is comprised of four subclasses: IgG1, IgG2, IgG3, and IgG4.
- IgG subclass deficiency—low IgG subclasses, more than two standard deviations below the mean value for age.
- Many individuals with IgG subclass deficiencies are asymptomatic (similar to IgA deficiency).
- Some with IgG subclass deficiencies exhibit reduced antibody responses to bacterial capsular polysaccharides and are prone to recurrent sino-pulmonary infections. This is most often seen in individuals with **IgG2** subclass deficiency with or without concomitant IgA deficiency.
- Most patients with recurrent infections can be managed with antibiotics alone.

Transient hypogammaglobulinaemia of infancy

- Gap between disappearance of maternally acquired Igs and production of own Igs.
- Low IgG levels at 3–12 months of age.
- Bacterial infections.
- Retrospective diagnosis (when antibody levels return to normal).
- Exclude diagnosis of SCID, XLA, and early-onset CVID.

X-linked hyper IgM (HIGM) syndrome

- Due to CD40 ligand deficiency; CD40L is a T-cell costimulatory molecule.
- Develop clinical features of antibody deficiency (see under XLA).
- Also develop infections characteristic of T-cell deficiency (*Pneumocystis* pneumonia, cryptosporidial infection—diarrhoea, ascending cholangitis, chronic liver impairment).
- Autoimmune diseases.
- Malignancy: lymphoma.
- IgG and IgA low, IgM high or normal.
- Neutropaenia is common.

- Treatment of antibody deficiency (as for XLA).
- Due to the high incidence of severe liver damage, allogeneic haematopoietic stem cell transplantation (HSCT), which is curative, should be considered in affected children.
- Rare autosomal recessive HIGM syndromes also exist.

Consequences of antibody deficiency

- Lung damage due to recurrent infections is the main cause of morbidity and mortality.
- There is also an increased incidence of autoimmunity and malignancy as described earlier.

Management of patients with antibody deficiency

Due to the occurrence of pathologies affecting multiple systems, patients are best managed in specialist immunology centres.

Lifelong immunoglobulin replacement is required—intravenous or subcutaneous.

Extent of associated pulmonary and gastrointestinal pathology needs to be assessed by appropriate investigation.

Replacement intravenous immunoglobulins (IVIG)

- 0.4g/kg every 3 weeks.
- Maintain pre-infusion trough IgG >8g/L.
- Higher doses may be required in those with structural lung damage and poor clinical response.
- Donor screening and viral inactivation steps used during manufacture help to ensure safety of Ig preparations.
- Nonetheless, Ig is a biological product which is associated with the theoretical risk of transmission of blood-borne infections.
- Many patients can be established on home therapy with Igs. Licensed subcutaneously infused Ig preparations are also now available.

Ancillary therapy

- Prompt treatment of infections with antibiotics is essential; higher doses and longer courses may be required.
- Inhalers and postural drainage may be required in those with chronic lung disease.

Primary T-cell immunodeficiency

DiGeorge syndrome

- One of the chromosome 22q deletion syndromes (hemizygous deletion 22q11.2).
- Has an incidence of 1/2500 live births, but the clinical phenotype is highly variable.
- Causes a complex inherited syndrome characterized by:
  - Learning difficulties.
  - Cardiac malformations.
  - Thymic hypoplasia.
  - Palato-pharyngeal abnormalities with associated velopharyngeal dysfunction.
  - Hypoparathyroidism (manifesting as hypocalcaemia).
  - Facial dysmorphism.
- About 20% of individuals with 22q deletion have thymic aplasia resulting in T-cell lymphopenia and impaired cell mediated immunity.
- In most, the degree of T lymphopenia is modest and complete recovery of the T-cell repertoire occurs by 2 years of age.
- Infections characteristic of T-cell deficiency are rare in these individuals.

Investigation

- CXR: absent thymic shadow, abnormal cardiac outline.
- Immunological deficiency: variable.
- T cell numbers: reduced.
- Lymphocyte proliferation: reduced.
- Chromosomal defect is detected by the technique called fluorescent *in-situ* hybridization (FISH).

Chronic mucocutaneous candidiasis

- Rare, both sexes affected.
- Chronic candida infection (skin, mucous membranes, nails).
- Autoimmune endocrine deficiency (hypoparathyroidism, Addison disease).
- T-cell responses to: C*andida*—poor; mitogens—normal.
- Antifungal therapy: regular, high dose, long periods.

Combined immunodeficiency

Severe combined immunodeficiency (SCID)

- Typically presents in first few weeks of life.
- Failure to thrive.
- Multiple severe infections caused by a broad range of microbial pathogens.
- **Absent lymphoid tissue**.
- Hypogammaglobulinaemia.
- Lymphopenia (absolute lymphocyte count $<2.5 \times 10^9$/L in 1st year of life is pathognomonic).
- Inheritance can be autosomal recessive or X-linked recessive.
- SCID can be caused by a large range of molecular defects.

Investigation

- Seek the advice of an immunologist.
- Determine absolute lymphocyte count.
- Enumerate T, B, and NK cells.
- Measure serum Igs.
- Rare cases without severe lymphopenia may need tests of lymphocyte function and assessment of lymphocyte clonality.

Management

- Invariably fatal in early infancy unless rescued by HSCT.
- The diagnosis constitutes a medical emergency needing urgent referral to a specialist centre which can confirm diagnosis and undertake bone marrow transplantation.
- HSCT with HLA-matched **sibling** donor can achieve cure rates of >80% (60% with matched **unrelated** donor).
- While awaiting referral to a specialist centre, the following steps are important:
  1. Investigate and treat infections.
  2. Barrier nursing.
  3. Avoid live vaccines (e.g. Bacillus Calmette–Guérin (BCG)).
  4. Commence treatment with IVIG.
  5. Start prophylaxis for *Pneumocystis*.
  6. Blood transfusions should be **irradiated** (to prevent graft-versus-host disease (GVHD) and from CMV-negative donors).

Wiscott–Aldrich syndrome

- X-linked disorder—loss of function of the WAS protein gene located at Xp11.22–23.
- Thrombocytopenia (small volume platelets).
- Eczema.
- Recurrent infections.
- Increased incidence of lymphoid malignancies.
- Low IgM, normal IgG and IgA.
- Poor response to polysaccharide antigens (e.g. pneumococcal capsular polysaccharide).
- Treatment of choice is HSCT.

Ataxia telangiectasia

- Autosomal recessive due to mutation in *ATM* (ataxia telangiectasia mutated) gene encoding a protein required for DNA repair.
- Defective DNA repair.
- Increased radiosensitivity.
- Neurological features: cerebellar ataxia, nystagmus.
- Telangiectases: conjunctiva, ear-lobes.
- Lymphoid malignancy: common in 2nd–3rd decade.
- Low IgA and IgG2.
- No curative therapy available.
- Needs management by multidisciplinary team in specialist centres.

Phagocytic disorders

Chronic granulomatous disease (CGD)

- Congenital defect of bacterial killing by phagocytic cells (neutrophils and monocytes).
- Oxidative pathway of microbial killing severely impaired due to defect in NADPH-oxidase complex.
- Develop subcutaneous, lymph node, pulmonary, and liver abscesses (Fig. 2.9).
- The spectrum of micro-organisms which cause infections in CGD include: *Staphylococcus aureus*, Gram-negative bacteria (*Burkholderia cepacea, Salmonella, Serratia*) and fungi (*Aspergillus* spp.)
- The formation of chronic granulomata in various tissues is a typical feature of CGD. In critical locations, granuloma formation may cause pathology (e.g. obstruction of the gastrointestinal or genitourinary tract).

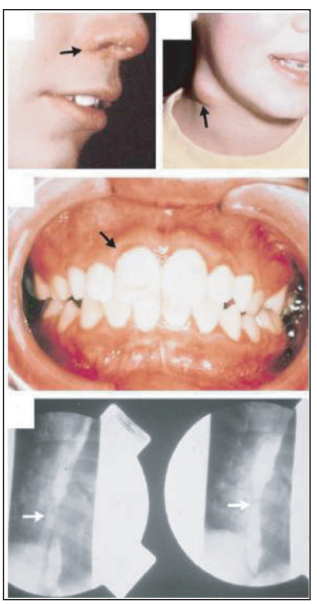


Fig. 2.9 Clinical features of chronic granulomatous disease (arrows indicate localized abscesses).

Top and middle figures: From *The New England Journal of Medicine, Lekstrom-Himes*, JA, and Gallin, JI, Immunodeficiency Diseases Caused by Defects in Phagocytes, 343 (23), Copyright © (2000) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Bottom figure: Reprinted from *The Journal of Pediatrics*, 111, 3, Chin TW et al., 'Corticosteroids in treatment of obstructive lesions of chronic granulomatous disease', pp. 349–352, Copyright (1987), with permission from Elsevier.

- Hepatosplenomegaly may occur (granulomatous infiltration).
- A granulomatous colitis resembling Crohn disease occurs in about 15%.

Investigation

- Test for phagocyte oxidase activity of blood neutrophils using nitro-blue tetrazolium test or equivalent flow-cytometric method.

Management

- Prophylactic antimicrobial therapy (bacteria, fungi).
- Usually treated with co-trimoxazole and itraconazole.
- IFN-γ therapy also reduces incidence of serious infections.
- Prompt and aggressive investigation and treatment of infections with bacteriological guidance important.

Cyclical neutropaenia

- Recurrent abscesses, mouth ulcers and fever at 3-weekly intervals.
- Neutrophil count $<1 \times 10^9$/L at time of infection.

Investigation

- Neutrophil count on alternate days for 4 weeks.

Management

- Prophylactic antibiotics (when neutrophil count is low).
- GM-CSF therapy (maintains normal neutrophil count).

Leucocyte adhesion deficiency

- Caused by defects in surface molecules on leucocytes (required for normal migration from the blood into the sites of infection).
- Patients typically present in **early childhood** with recurrent pyogenic infection of skin, respiratory, and gastrointestinal tracts.
- Older children have severe gingivitis and periodontal disease.
- Poor wound healing and delayed umbilical cord separation are typical.
- Due to impaired neutrophil migration, these patients develop a leucocytosis and pus fails to form at sites of infection.
- These inherited disorders are rare.

Investigation

- Flow cytometry of blood leucocytes for expression of leucocyte adhesion molecules (CD18 or rarely CD15).

Management

- Prognosis is poor without HSCT.

Type 1 cytokine pathway defects

- Some bacterial species (*Mycobacteria, Salmonella*) can grow and multiply within macrophages. The elimination of these organisms depends on activation of bactericidal mechanisms operating within macrophages by the cytokine IFN-γ.
- On exposure to these pathogens, macrophages and dendritic cells secrete the cytokine IL-12 which in turn stimulates T cells and NK cells to secrete IFN-γ.
- Patients with defects in the IL-12-dependent IFN-γ axis develop disseminated infections caused by mycobacterial species of low-grade virulence (NTM, BCG) or *Salmonella*.
- Such patients may have a defect in IL-12, IL-12 receptors or IFN-γ receptors.

Investigation

- The functional integrity of the IL-12 dependent IFN-γ pathway needs to be assessed in patients with disseminated NTM/BCG or *Salmonella* infections.
- Seek the advice of an immunologist.

Management

- Patients with **complete** IFN-γ receptor defects present in early infancy with NTM or BCG infections. Prognosis is poor unless treated with a bone marrow transplant.

- **Partial** IFN-γ receptor defects and defects in IL-12 or IL-12 receptors usually present later in life and usually respond to prolonged courses of antibiotics.
- If response to antibiotics is poor, they can be treated with recombinant IFN-γ.

Complement pathway deficiencies

See Table 2.4.

Table 2.4 Complement pathway deficiencies

Complement deficiency	Clinical association
C1q, C1r, C1s, C4, C2	SLE, immune complex disorders
C3 properdin, membrane attack complex proteins (C5, C6, C7, C8, C9)	Neisserial infection
C1 inhibitor	Angio-oedema
CD59	Haemolysis, thrombosis
C3	Pyogenic bacterial infections (may be accompanied by distinctive rash) Membranoproliferative glomerulonephritis
Factor H and factor I	Haemolytic uraemic syndrome Membranoproliferative glomerulonephritis

From *The New England Journal of Medicine*, Walport M.J, Com plement, 344 (14), Copyright © (2001) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Splenectomy

- Main indications:
  - Splenic trauma.
  - Hypersplenism.
  - Autoimmune haemolysis.
  - ITP.
  - Congenital haemolytic anaemia.
- Post-splenectomy blood film: Howell–Jolly bodies, target cells.
- Lifelong increased risk from infection: mainly from **encapsulated** organisms which are normally cleared from the circulation by the spleen (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides, Capnocytophaga canimorsus*, the latter almost exclusively after dog bites or dog scratches).

Management

- Vaccinations:
  - Pneumococcal (every 5–10 years, or when antibodies fall below protective level).
  - *Haemophilus influenzae* type b.
  - Meningococcal C.
  - Influenza (yearly).
- MedicAlert bracelet.
- Prophylactic oral antibiotics (lifelong), phenoxymethyl-penicillin (erythromycin if penicillin allergic).
- Seek urgent medical attention if signs of infection.
- International travel—risk of severe malaria (appropriate malaria prophylaxis and mosquito avoidance measures advised).

2.8 Immunology investigations

Immunoassays

ELISA (enzyme-linked immunosorbent assay)

Method

- Antigen bound to solid phase (bead/plate).
- Reacted with serum.
- React with anti-serum against human Ig coupled to enzyme.
- React with substrate (direct or amplification).
- Spectrophotometric reading taken.
- Pros: more sensitive, can automate.
- Cons: may lose specificity, pure antigen required (recombinant), commercial kit based assays may be costly.

Radioimmunoassay

- Highly sensitive.
- Requires pure antigen/radioisotopes.
- Laboratories are moving away from using this technique.

Fluoroimmunoassay

Method

- Antigen bound to solid phase (bead/plate).
- Reacted with serum.
- React with anti-serum against human Ig coupled to fluorescent dye or its precursor.
- React with substrate (direct or amplification).
- Fluorescence readout.

Immunochemistry

Examples of assays

- Serum immunoglobulins and electrophoresis.
- Urinary protein analysis.
- Specific antibodies.
- Total and allergen-specific IgE.
- Assays for complement components.
- Measurement of acute-phase reactants.

Serum immunoglobulins

- Levels vary according to age.
- Polyclonal elevation: chronic infection/inflammatory disorders, liver disease, autoimmune disease.
- Monoclonal elevation: myeloma/monoclonal gammopathy of uncertain significance (MGUS), Waldenström macroglobulinaemia, lymphoma.

Serum electrophoresis

- Separates proteins according to electrical charge.
- Main use is to detect paraproteinaemia.
- Densitometry: measures size of paraprotein band.

Urinary protein analysis

- Urine electrophoresis: concentrated urine used.
- Urinary free light chains: spot morning urine or 24-hour sample (no preservative).

Immunoblotting

Method

- Antigens electrophoresed in a matrix or applied to a matrix.
- Incubate with dilutions of serum.
- Enzyme-conjugated anti-serum added.
- Substrate added.
- Read out: coloured band.
- Pros: quick, can automate.
- Examples: ENA/PR3/MPO/M2 mitochondrial assays.

Immunoprecipitation assay

Principle

- Antigen meets antibody at optimum concentration.
- Forms insoluble immune complex.
- Solid phase:
  - Double diffusion (DD).
  - Counter-current immunoelectrophoresis (CCIE).
- Liquid phase:
  - Nephelometry/turbidometry (automated analysis possible).

Immunofluorescence

Indirect immunofluorescence

Method

- Tissue substrate on glass slide (rodent/human).
- Patient serum incubated with slide.
- Conjugated anti-human Ig added.
- Read using a fluorescence microscope.

Examples

- Autoantibodies (ANA (see Fig. 2.10), AMA, SMA, endomysial, adrenal).

Direct immunofluorescence

Method

- Tissue biopsy on slide (renal or skin).
- Conjugated anti-human Ig.
- Read using a fluorescence microscope.

Cellular immunology

Lymphocyte phenotyping

- Flow cytometric assay.
- Lymphocyte sub-populations (T, B, and NK cells).
- Panel of monoclonal antibodies directed at CD markers.
- Age-appropriate ranges.
- Immunodeficiency and lymphoid malignancy panels.
- Serial CD4+ measurements, e.g. HIV monitoring—**not** to be used as a surrogate for HIV diagnosis.

Lymphocyte proliferation tests

Method

- Heparinized blood.
- Incubate for 3–5 days with: mitogens or antigens (*Candida*, tetanus).
- Cell proliferation detected by 3H-thymidine incorporation or equivalent non-isotopic test.

Indications

- SCID/DiGeorge syndrome.

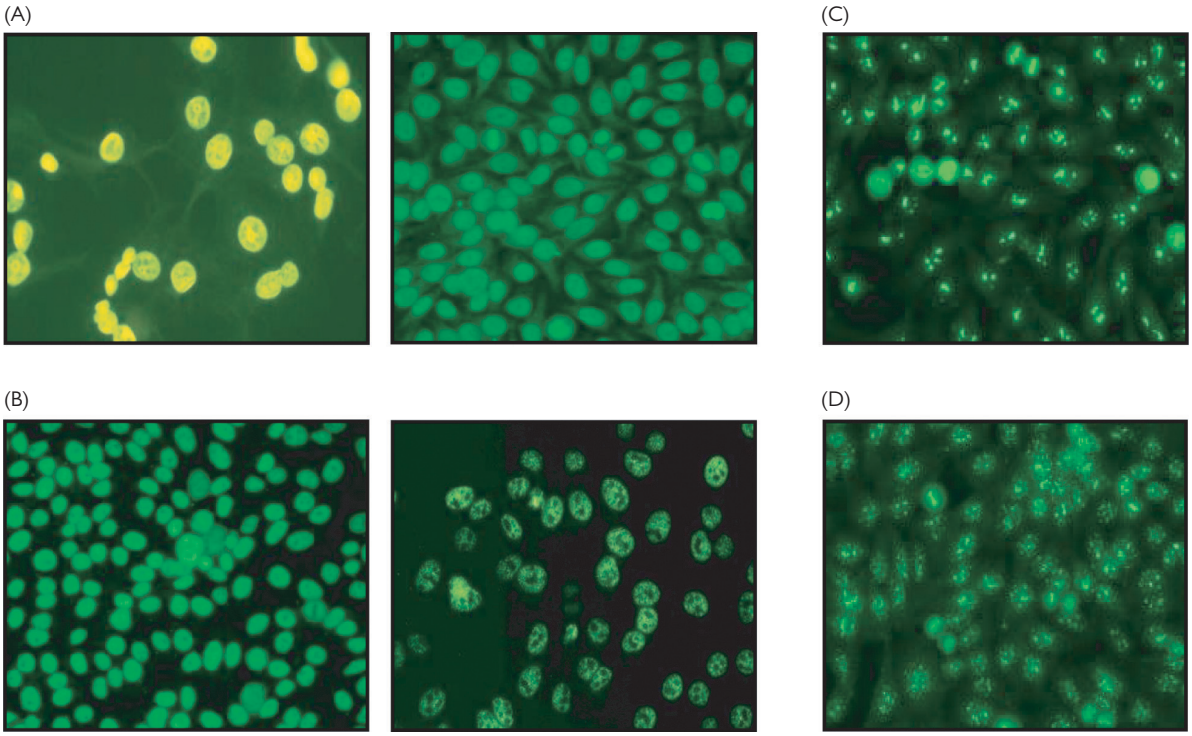


Fig. 2.10 Antinuclear antibody patterns (ANA). (A) Homogeneous. (B) Speckled. (C) Nucleolar. (D) Centromere.

Neutrophil function tests

Indications

- Recurrent skin infections.
- Chronic gingivitis.
- Recurrent deep-seated bacterial/fungal infections.

Types of assays

- Oxidative burst test assays.
- Nitro blue tetrazolium assay.
- Flow cytometric assay: di-hydro rhodamine test.
- Adhesion molecule assay.
- CD18 and CD15 expression by flow cytometry.

2.9 Immunological therapies

Immunosuppressive drugs

- Used in the treatment of autoimmunity, allergy, and transplant rejection.
- Most also suppress immune responses to pathogens.
- Specific tolerance not possible resulting in an increased infection risk.

Corticosteroids

- Very widely used.
- Affect many cell types.
- Cause a wide range of side effects including metabolic, cardiovascular, musculoskeletal, and neurological disturbance.

Azathioprine

- Inhibits purine synthesis which is essential for proliferation of many cell types (especially T cells).
- Converted in the body to the active metabolites 6-mercaptopurine (6-MP) and 6-thioinosinic acid.
- Used alone in many disorders and in combination with other immunosuppressants in organ transplantation.
- Side effects are uncommon but include: nausea, rash, haemolytic anaemia, and bone marrow suppression (remember to avoid co-administration with allopurinol).
- Thiopurine S-methyltransferase (TPMT) deactivates 6-MP and genetic polymorphisms can lead to drug toxicity. Serum TPMT assays may be useful to prevent this complication.

Mycophenolate mofetil (MMF)

- Also inhibits purine synthesis essential for the proliferation of T and B lymphocytes.
- Increasingly being used in favour of azathioprine in organ transplantation, and in the treatment of various autoimmune diseases.

Cyclophosphamide

- Alkylating agent cross-links DNA.
- Especially toxic to B cells.

Indications

- Malignancy.
- Severe autoimmune disease (SLE, vasculitis).

Adverse effects

- Neutropaenia, lymphopenia.
- Alopecia, infertility (especially ♀).
- Haemorrhagic cystitis (to prevent: increase fluid intake and consider mesna).

Methotrexate

- Inhibit dihydrofolate reductase (folic acid not converted to active form—tetrahydrofolate).

Indications

- Malignancy: leukaemia.
- Inflammatory disorders: RA, psoriasis, polymyositis.
- GVHD.
- Steroid-dependent asthma.

Adverse effects

- Bone marrow suppression, megaloblastic anaemia.
- Mucositis, pneumonitis.
- Hepatic impairment.
- Folinic acid rescue for acute adverse effects.

Ciclosporin

- Interacts with immunophilins.
- Prevents signalling following T-cell receptor activation.
- Narrow therapeutic range: therapeutic drug monitoring required to assess risk of toxicity.
- Reduces incidence of transplant rejection.
- Significantly improves graft survival.

Adverse effects

- Hirsutism, gum hyperplasia (common: especially with poor oral hygiene and nifedipine co-administration).
- Hypertension, nephrotoxicity (dose-dependent).
- Liver dysfunction, fluid and potassium retention.
- Burning hands and feet (especially during the first week of therapy).
- Skin and lymphoid malignancy (with long-term therapy).
- Grapefruit or grapefruit juice should not be taken for 1 hour before the dose of ciclosporin.

Tacrolimus

- Macrolide.
- Binds cytosolic FK506 binding protein (FKBP).
- Prevents *IL-2* gene activation.

Indications

- Renal and liver transplantation.
- Autoimmune disease.
- Atopic dermatitis (topical).

Adverse effects

- Similar to ciclosporin.
- Most common adverse events associated with topical tacrolimus includes: sensation of skin burning, itching, flu-like symptoms, and headache.

Sirolimus

- Binds specific protein tyrosine kinase.
- Inhibits signals after IL-2 has bound to its receptor.

Monoclonal antibodies

Infliximab

- Chimeric monoclonal antibody to tumour necrosis factor alpha (TNF-α).
- Uses: Crohn disease, RA, ankylosing spondylitis.
- Dose: 3mg/kg IV infusion, repeated at intervals of 2–8 weeks.

Adverse effects

- Increase risk of tuberculosis (screening important).
- Production of ANA.
- Production of human anti-chimaeric antibody (HACA) which reduces the therapeutic effect minimized by combined use with methotrexate.

Adalimumab

- Human monoclonal antibody to TNF-α.
- Often co-administered with methotrexate.
- 40mg subcutaneous dose on alternate weeks.
- Indications and side effects: similar to infliximab.

Etanercept
- Soluble fusion protein of TNFR2 and Fc portion of human IgG1.
- Binds TNF-α, TNF-β.
- Synergistic with methotrexate.
- Indications: RA, psoriatic arthritis.
- Subcutaneous administration.
- Increased risk of infection (including varicella zoster).

Rituximab
- Humanized anti-CD20 monoclonal antibody.
- Depletes B cells.
- IV infusion administration.

Uses
- Advanced follicular lymphoma (and other types).
- Inflammatory disease: RA, SLE, systemic vasculitis.
- Adjunctive therapy in ABO-incompatible organ transplantation.

Adverse effects
- Cytokine release syndrome.
- Arrhythmia, heart failure.
- Pre-medicate: antihistamines, steroids.

Anakinra
- Recombinant IL-1R antagonist.
- Blocks action of IL-1.
- 100mg/day, subcutaneous administration.
- Indications: RA, auto-inflammatory disorders.
- Adverse effects: neutropaenia, headaches.

Omalizumab
- Murine anti-human IgE monoclonal antibody.
- Inhibits IgE binding to its receptor.
- Blocks IgE mediated release of inflammatory mediators from mast cells.
- Indications: moderate-severe asthma, allergic conjunctivitis and rhinitis, food allergy.

Basiliximab
- Monoclonal antibody against the IL-2 receptor on T cells.
- T cells are unable to proliferate.
- Used as induction therapy for organ transplantation (especially renal) to prevent rejection.

Immunoglobulin therapy (IVIG)

Replacement therapy for antibody deficiency
- Dose: 0.2–0.6g/kg body weight every 4 weeks.

High-dose IVIG therapy

Mechanism of action
- Fc receptor blockade.
- Inhibits macrophage activation.
- Inhibits T-cell activation.
- Alters networks pertinent to autoreactivity and induction of tolerance to self.
- Dose: 1–2g/kg.

Uses
- Autoimmune thrombocytopenia.
- Kawasaki disease.
- Guillain–Barré syndrome.
- Dermatomyositis.
- Multifocal motor neuropathy.

Adverse effects
- Aseptic meningitis.
- Acute haemolysis.
- Deterioration in renal function.

Cytokine therapy

Interferon-α
Indications
- Lymphoma, leukaemia.
- AIDS-related Kaposi sarcoma.
- Renal cell carcinoma.
- Chronic hepatitis B and C infection.
- Administered subcutaneously.

Adverse effects
- Influenza-like syndrome.
- Bone marrow suppression.
- Hepatic/renal toxicity.

Interferon-β

Indications
- Relapsing-remitting multiple sclerosis (MS)—benefits some, may cause deterioration in others.
- Administered subcutaneously.

Adverse effects
- Local irritation at injection site.
- Influenza-like symptoms.
- Hypersensitivity reaction (anaphylaxis, urticaria).

Interferon-γ

Indications
- CGD.
- IFN-γ/IL-12 pathway defects.
- Administered subcutaneously, three times a week.
- Dose based on body surface area.

Adverse effects
- Influenza-like symptoms.
- Anaemia.
- Abnormalities in liver/renal function.

Granulocyte macrophage colony-stimulating factor (GM-CSF)
- Increases the production of mature neutrophils.

Indications
- Chemotherapy/neutropaenic sepsis.
- To mobilize stem cells (stem cell harvest).
- Congenital neutrophil disorders (cyclical neutropaenia).

Adverse effects
- Increased risk of myeloid malignancy.
- Bone pain.

Chapter 3

Cardiovascular medicine

3.1 Basic science

Introduction

Cardiovascular disease remains the most common cause of death worldwide. Despite advances in primary and secondary preventive treatment, mortality from ischaemic heart disease remains high in the developed world and is increasing in developing countries. There is wide geographical variation in other cardiac disorders, such as rheumatic fever and endomyocardial fibrosis. A precise understanding of normal cardiac structure and function is essential to understanding the pathophysiology and treatment of cardiovascular disorders (Fig. 3.1).

Normal cardiac rhythm

The cardiac cycle begins with atrial depolarization, originating in the normal heart in the sinoatrial (SA) node.

Normal cardiac conduction depends on the integrity of:

- SA node.
- Internodal fibres.
- Atrioventricular (AV) node.
- AV bundle (of His).
- Ventricular Purkinje fibres.

The cardiac cycle

The cardiac cycle can be represented graphically as the pressure–volume relationship of the left ventricle (Fig. 3.2).

Notable points

- Atrial systole ('a' on Fig. 3.2) boosts left ventricular (LV) filling at the end of diastole, and is particularly advantageous in impaired ventricular filling (e.g. when the left ventricle fails to relax normally, such as in LVH).
- Isovolumetric contraction begins when LV pressure exceeds atrial pressure, and continues until it exceeds aortic pressure.
- **Physiological** systole lasts from the start of isovolumetric contraction to the peak of the ejection phase.
- **Cardiological** systole lasts from closure of the mitral valve to closure of the aortic valve (i.e. between heart sounds S1 and S2).

Heart sounds

The timing of the heart sounds in relation to the cardiac cycle is shown in Fig. 3.2:

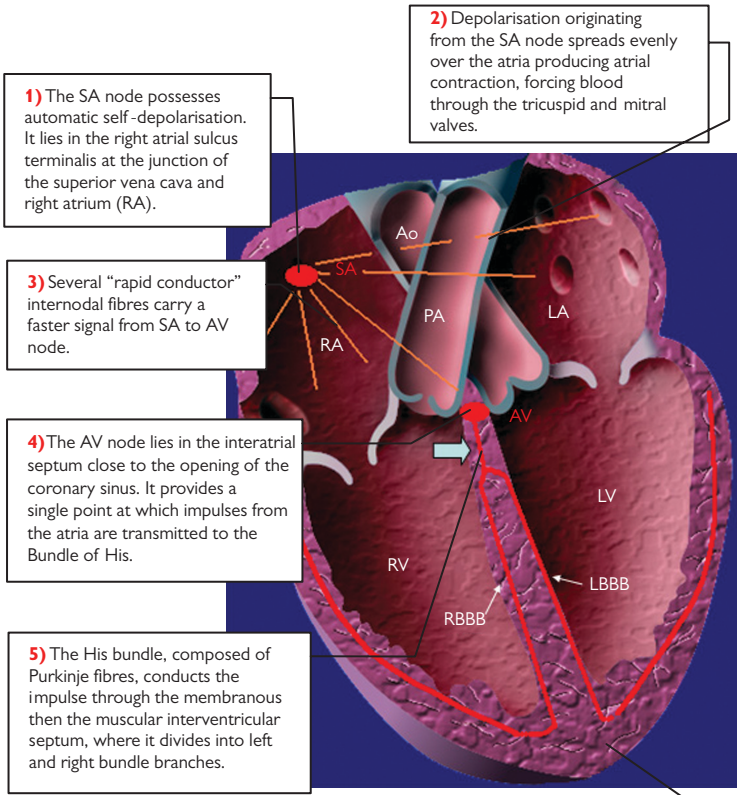


Fig. 3.1 Anatomy of the cardiac conducting system.

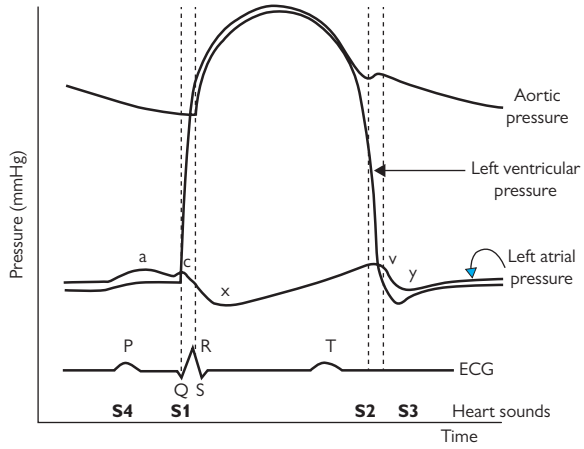


Fig. 3.2 The cardiac cycle. The changes in left ventricular (LV), aortic, and left atrial pressures during the cardiac cycle (timed against the ECG), and the timing of the heart sounds (including S3 and S4 if present). Atrial depolarization ('P' wave on ECG) is closely followed by atrial contraction at the end of diastole ('a' wave—see section on JVP). Systole begins with a brief period of isovolumetric ventricular contraction (between first set of dotted vertical lines) followed by ejection of blood into the aorta (once LV pressure exceeds aortic). The ejection phase ends when LV pressure falls below aortic pressure and the aortic valve closes; a brief period of isovolumetric ventricular relaxation (between second set of dotted vertical lines) follows, until the atrioventricular valves open and passive ventricular filling resumes.

- S1 corresponds with closure of the mitral and tricuspid valves, while closure of the aortic and pulmonary valves corresponds with the A2 (aortic) and P2 (pulmonary) components of S2 respectively.
- The interval between A2 and P2 is caused by the variation of venous return to the right heart with respiration.
- Wider separation ('splitting') of A2 and P2 can occur in certain pathological states.
- S3 is caused by passive ventricular filling as soon as the mitral and tricuspid valves open. S3 can be normal in those <40 years old, but can also occur in LV dilatation, significant mitral or tricuspid regurgitation, constrictive pericarditis, or ventricular septal defects.
- S4 is caused by atrial systole, propelling blood into a stiff left ventricle. Any cause of decreased LV elasticity (e.g. LVH, infiltrative diseases) can cause an audible S4; rarely, it can be heard in the acute myocardial infarction (MI) setting.

See Box 3.1 for abnormalities of S1 and S2.

Arterial pulse

Abnormalities of arterial pulse character are common MRCP (membership of the royal colleges of physicians) questions. In summary: An exaggeration of the normal drop in systolic (and pulse) pressure during inspiration; >10mmHg is pathological.

Slow rising	Aortic stenosis.
Collapsing	Aortic incompetence, patent ductus arteriosus, hyperdynamic circulation (e.g. anaemia, thyrotoxicosis).
Bisferiens	Mixed aortic valve disease (aka biphasic—the pulse has a palpable double peak).
Alternans	Alternating strong and weak beats: severe LV failure, can occur in tachyarrhythmias in a normal heart.
Bigeminus	Premature ectopic after each sinus beat (benign in the absence of ischaemic or structural heart disease).
Jerky	LV outflow tract obstruction.
Paradoxus	Asthma, constrictive pericarditis, tamponade.

Box 3.1 Abnormalities of S1 and S2

S1

Loud	Soft
Short P–R interval	Long P–R interval
Mitral stenosis (mobile)	Mitral stenosis (immobile)
Tachycardic states	Mitral regurgitation
Hyperdynamic states	Hypodynamic states

Tachycardia

S1 can be split on normal inspiration; pathological causes of splitting of S1 include: right (RBBB) and left bundle branch block (LBBB), ventricular tachycardia.

S2

Loud	Soft
Systemic hypertension Pulmonary hypertension Atrial septal defect Tachycardia	Advanced aortic stenosis

Physiological splitting of S2 occurs on inspiration and is normal. Abnormal splitting can occur:

- **Fixed:** atrial septal defect.
- **Wide:** RBBB, deep inspiration, pulmonary stenosis, mitral regurgitation.
- **Reverse** (i.e. splitting increases on expiration): systemic hypertension, LBBB, aortic stenosis, patent ductus arteriosus, right ventricular pacing lead.

Jugular venous pulse

The jugular venous pulse (JVP) acts as a 'manometer' of right atrial pressure. As there are no valves between the internal jugular system and the right atrium, the JVP directly reflects pressure changes within the right atrium. Examination of the JVP is an essential component of clinical cardiovascular assessment and is outlined in Fig. 3.3 and Box 3.2.

The external jugular vein may be distended when the central venous pressure is elevated, but it is an unreliable marker as it not only contains valves, but also may be kinked as it passes through the deep fascia of the neck.

An abnormally low JVP—usually caused by severe hypovolaemia—cannot be measured clinically.

Normal waveform

The normal JVP waveform consists of three peaks (*a*, *c*, and *v* waves) and two troughs (*x* and *y* waves; see Fig. 3.3). These coincide with specific events in the cardiac cycle (Fig. 3.2):

- *a* **wave:** atrial systole (may cause an audible S4 if prominent); absent in atrial fibrillation.
- *x* **descent:** drop in JVP that begins as soon as atrial contraction has ceased.
- *c* **wave:** very difficult to see—no more than a flicker during the *x* descent. Caused by rapid increase in right ventricular pressure just before tricuspid valve closes, transmitted retrogradely up the internal jugular vein. In practice, the *c* wave signifies closure of the tricuspid valve.
- *v* **wave:** passive filling of the right atrium during ventricular systole (tricuspid valve closed) leads to a gradual increase in right atrial pressure, the peak of which corresponds to the *v* wave.
- *y* **descent:** passive draining of blood from right atrium to ventricle through the tricuspid valve; if prominent, an S3 may be audible.

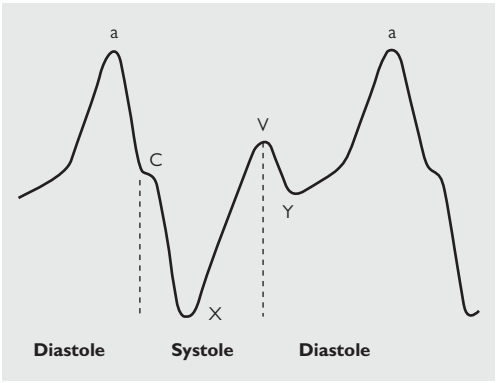


Fig. 3.3 Jugular venous pulse waveform.

Causes of a raised JVP

The JVP may be raised with a normal waveform, or else individual components of the waveform may be abnormal. An elevated JVP that paradoxically rises with inspiration is termed Kussmaul sign, caused by cardiac tamponade, constrictive pericarditis, or right ventricular infarction. Superior vena cava obstruction (e.g. by tumour) causes a highly elevated, pulseless JVP with no respiratory variation.

Raised JVP with normal waveform

- Fluid overload.
- Right heart failure.
- Marked bradycardia.

Raised JVP with abnormal waveform

a waves can be:

- **Giant:** tricuspid stenosis (although often in atrial fibrillation hence no *a* waves), pulmonary stenosis, pulmonary hypertension. Marked hypertrophy of the ventricular septum (e.g. hypertrophic cardiomyopathy) can encroach on the right ventricular cavity, obstructing right ventricular filling (Bernheim effect).
- **Cannon:** occur when the right atrium contracts against a closed tricuspid valve; the high pressure generated causes a rapid rising—and larger—*a* wave, e.g. complete heart block, ventricular extrasystoles, ventricular tachycardia, 2:1 2nd-degree heart block, junctional rhythms.
- **Absent:** atrial fibrillation.

x descent

In states of extrinsic myocardial compression (e.g. constrictive pericarditis, tamponade), passive filling of the right atrium can only occur during ventricular systole; a steep *x* descent ensues.

Giant v waves

Tricuspid regurgitation (TR): throughout ventricular systole right ventricular pressure is transmitted directly to the right atrium/IJV. With mild-moderate TR, elevated or giant v waves are seen, becoming a single sinusoidal waveform (systolic *cv* waves) with severe TR. Associated with pulsatile hepatomegaly.

y descent can be:

- **Rapid:** rapid flow through the tricuspid valve as soon as it opens (tricuspid regurgitation, cardiac tamponade).
- **Slow:** tricuspid stenosis.

Normal cardiac function and exercise

Changes in both systolic and diastolic function occur during exercise. The effects of exercise on LV pressure and volume are shown in Fig. 3.4.

Systolic function

- Vagal withdrawal causes the initial increase in heart rate.
- Sympathetic nervous system promotes a further increase in heart rate and increases contractility.
- Left and right ventricular end-diastolic volumes (EDVs) rise slightly while end-systolic volumes (ESVs) decrease.
- Stroke volume, ejection fraction, and cardiac output (CO) increase.
- Mild exercise—CO increase is due to increases in both heart rate and stroke volume; more severe exercise—CO increase is driven predominantly by increase in heart rate.

Diastolic function

- Less well studied than systolic function.
- LV ESV is smaller in exercise, but rate of LV relaxation in diastole is increased.

Box 3.2 Examination of the JVP

- Maximal pulsation of the internal jugular vein (IJV) (usually) occurs when the trunk is inclined at 45° to the horizontal; therefore this angulation is most commonly used in clinical examination.
- If central venous pressure is highly elevated, sit the patient up further.
- Patient must be allowed to relax; the IJV runs deep to the strap muscles on anterior neck and is difficult to see if they are tensed.
- Ask the patient to turn their head slightly to the left or right. Shining a light (bedside lamp) tangentially across the skin overlying the IJV makes pulsation more obvious.
- The contralateral carotid pulse can be palpated simultaneously to allow timing against events of the cardiac cycle (*a* wave occurs just before carotid pulse; *v* wave accompanies carotid pulse).
- Vertical height of the JVP column (from the sternal angle ('angle of Louis') which provides a fixed reference point to the midpoint of the right atrium) is measured.
- The JVP should be ≤4cm above the angle of Louis in health; corresponds to the JVP being just visible above the clavicle.
- CVP = JVP + 5cmH_2O.

Venous or arterial pulse?

The following features help differentiate the JVP from carotid pulse:

- It is not palpable.
- It is obliterated by finger pressure.
- The pulsation is upwards rather than outwards.
- Rises transiently with pressure applied to the abdomen below the right costal margin (hepatojugular reflux (not reflex)).
- Alters with posture (falls as patient sits up) and respiration (falls with deep inspiration).
- Double waveform for every arterial pulse.

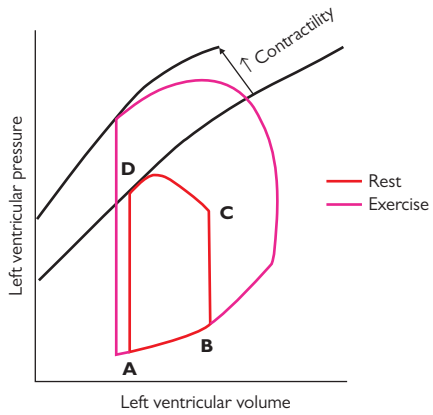


Fig. 3.4 Left ventricular volume/pressure curve at rest and during exercise.

- The 'elastic recoil' of the left ventricle is therefore increased in exercise.
- This creates a 'diastolic suction effect' which allows more rapid LV filling during diastole—one-third of the stroke volume may enter the left ventricle while the LV pressure is still falling.

Abnormalities of systolic or diastolic function may lead to the syndrome of heart failure (see Section 3.5).

During ventricular diastole, passive filling of the left ventricle results in a gradual increase in LV volume and mild increase in pressure (AB in Fig. 3.4). Once the atrioventricular valves close, there is a period of isovolumetric ventricular contraction during which LV pressure rises steeply (BC); once the aortic and pulmonary valves open, LV pressure continues to rise but volume falls as blood is ejected into the aorta (systole—CD). At the end of systole, these two valves close and there is a period of isovolumetric ventricular relaxation (DA). The increased stroke volume, enhanced contractility, and higher LV pressures that occur during exercise in a normal heart are shown in Fig. 3.4.

3.2 Cardiovascular investigation

Electrocardiology

The electrocardiogram (ECG)

The recording of an ECG is a simple, cheap, non-invasive means of providing immediate information about the cardiac status of a patient, yet the ECG contains more information than is appreciated by most physicians. A structured methodology in ECG interpretation, which is beyond the scope of this book, is required, together with knowledge of key 'checklists' of causes of common ECG abnormalities.

Cardiac intervals

PR interval

- Normal range 120–200ms.
- Can be abnormally short or long.
- Short PR interval usually indicates pre-excitation via an accessory pathway (e.g. Wolff–Parkinson–White (WPW) syndrome) but may also be caused by low atrial rhythms, nodal rhythms, ventricular extrasystoles; rarely Duchenne muscular dystrophy and glycogen storage disorders.
- Prolongation of the PR interval suggests first-degree heart block (see Section 3.4).

QRS complex duration

- Normal if <120ms.
- Prolongation of the QRS duration suggests a conduction defect within the ventricles.
- Most commonly, the typical left or right bundle branch block (BBB) pattern will be present (Table 3.1).
- If QRS >120ms but the typical RBBB or LBBB pattern is not present, a non-specific intraventricular conduction defect (IVCD) is said to be present.
- Incomplete or 'partial' BBB present if the QRS complexes display the typical BBB morphology but QRS <120ms.
- R wave dominance in V1 is a common MRCP question (Box 3.3)

QT interval

- Affected by heart rate hence usually corrected for this.
- Bazett formula corrects QT (QTc) using interval between the peaks of successive R waves (the RR interval):
  $QTc = QT/\sqrt{RR}$
- Normal QTc = 380–420ms.
- Prolongation can be congenital or acquired (see Box 3.4 and Fig. 3.5).

Cardiac axis

Can be deviated to the left (LAD) or right (RAD). See Table 3.2 for causes.

Table 3.1 Causes of bundle-branch block

LBBB	RBBB
Ischaemic heart disease	Normal variant
Acute MI	Idiopathic
Severe coronary disease*	Coronary artery disease*
LV outflow tract obstruction	RV strain
Aortic stenosis	Atrial septal defect (ASD)
Severe LVH	Myocarditis
Myocarditis	RV cardiomyopathy
Cardiomyopathy	
RV pacemaker lead	

* LBBB and RBBB suggest more severe coronary disease.

Box 3.3 R wave dominance in lead V1

More common in examinations than in clinical practice!
Causes include:

- True posterior myocardial infarction.
- WPW type A syndrome.
- RBBB.
- RVH.
- Duchenne muscular dystrophy.
- Hypertrophic cardiomyopathy.
- Dextrocardia.
- Dextroposition (e.g. due to right basal atelectasis).

ST segment

The ST segment deviation is measured as the vertical shift of the ST segment from the isoelectric line, at a point 80ms beyond the J point (where the QRS complex ends) (Box 3.5).

Early repolarization or 'high take-off' often confuses junior and senior doctors alike. It typically occurs in healthy young males. The T wave begins early, resulting in elevation of the ST segment at the J point. It is best seen in leads V1–V3 and is benign (Fig. 3.6). It is very difficult to differentiate from ST elevation due to acute infarction, hence it is safer to assume the latter if the patient has a chest pain history.

Ambulatory ECG recording

While many dysrhythmias are relatively benign, several are malignant yet cause only intermittent symptoms. Ambulatory ECG monitoring is a key component of the investigation of arrhythmias, syncope/presyncope, and response of arrhythmias to treatment. Four main categories:

Holter monitors (Inventor: Dr Norman Holter)

- Continuous ECG recording (24–48 hours).
- Requires the continuous attachment of recorder via three or more electrodes to skin.

Box 3.4 Causes of long QT syndrome (LQTS)

Congenital

Drug-induced

- Quinidine, procainamide, N-acetylprocainamide,disopyramide
- Amiodarone, bretylium, sotalol
- Amitriptyline and other tricyclics
- Erythromycin and other macrolides
- Chlorpromazine and other phenothiazines
- Cisapride
- Non-sedating antihistamines (astemizole, terfenadine)
- Probucol

Metabolic/electrolyte disturbances

- Hypokalaemia
- Hypocalcaemia
- Hypomagnesaemia
- Hypothermia

Other

- Starvation
- CNS lesions (e.g. subarachnoid haemorrhage (SAH))
- Cardiac ganglionitis
- Mitral valve prolapse

Note: <http://www.sads.org.uk/drugs_to_avoid.htm> provides an extensive list of causative medications

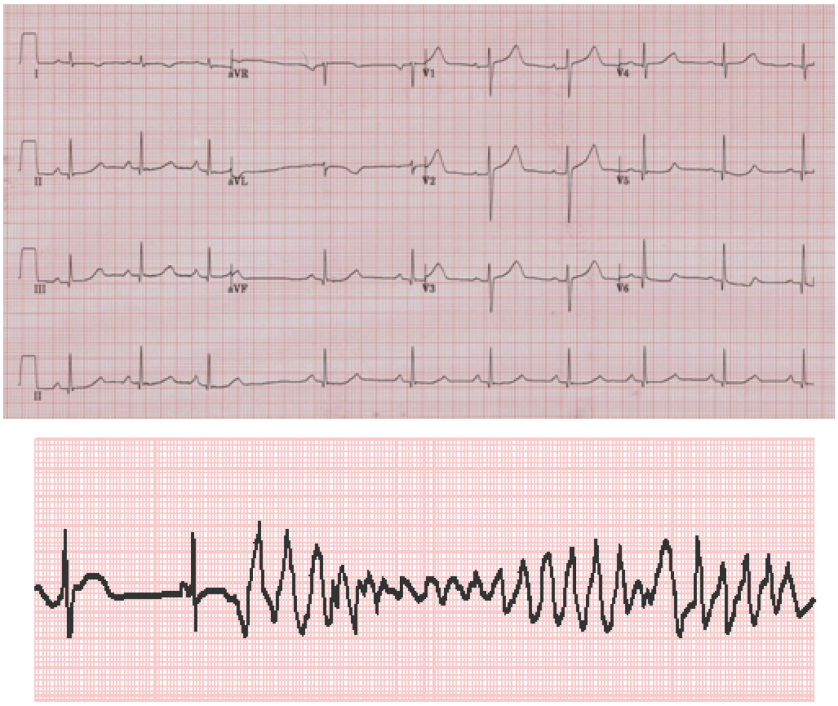


Fig. 3.5 Long QT syndrome: QTc = 510ms.

- Tape recorder, or in modern systems solid-state storage systems (flash cards) used to store data prior to analysis.
- Useful if daily symptoms but low detection rate if symptoms infrequent.

Event recorders

- Can be used for up to 30 days so useful if patient's symptoms weekly/monthly.
- Do not have to be worn constantly but patients encouraged to wear as much as possible.
- Older devices need activation during symptoms and then 'phoned-in' to cardiology department for analysis.
- Not useful if symptoms very brief, or if patient experiences syncope without premonitory symptoms.

External loop recorders

- Can be used for up to 30 days.
- Continuously record and delete ECG; activation (by pressing button) will 'freeze' recording and store ECG from 1–4 minutes before activation until 30–60 seconds afterwards.
- Newer models can be programmed to store ECG automatically if heart rate outside pre-set parameters.

Implantable loop recorders

- Can be used for up to 24–30 months dependent on model.
- Involves implantation of recorder (Fig. 3.7) in subcutaneous pocket on left anterior chest wall.
- Reserved for those with infrequent but severe symptoms who have undergone unrevealing Holter/event monitors.
- Can be activated by patient but also activate automatically.

Certain pacemakers, and implantable cardioverter defibrillators, can record significant rhythm disturbances also.

Congenital LQTS

- Two major forms of congenital LQTS: Romano–Ward (autosomal dominant) and Jervell–Lange–Nielsen (autosomal recessive, associated with deafness) syndromes.
- >250 mutations in multiple genes have been described in congenital LQTS (numbered LQTS 1–13; LQTS 1–3 account for most disease cases).
- Presents as syncope or sudden cardiac death (SCD), often during physical exertion; other triggers include emotion and sudden 'startling' or loud noises, e.g. alarms.
- Higher risk of SCD: those with family members who died suddenly at an early age; those with syncope.
- Variation in 'risk' between mutations—LQTS 1 and 2 have highest risk of arrhythmias. LQTS 3 is associated with fewer cardiac events but they are more likely to be lethal.
- LQTS 1 and 2 events are associated with sympathetic activation (e.g. exercise); LQTS 3 events with sleep.

Table 3.2 Causes of left and right axis deviation

LAD	RAD
Left anterior hemiblock	Left posterior hemiblock
LBBB	RBBB (rarely LBBB*)
LVH	RVH
Primum ASD	Secundum ASD
Tricuspid atresia	Infancy

*LBBB can rarely be associated with right axis deviation.

Box 3.5 Causes of ST shift on 12-lead ECG

ST elevation	ST depression
Acute MI Myopericarditis LV aneurysm	Normal variant: fixed change; sinus tachycardia-induced J-point depression
Variant angina (formerly Prinzmetal—coronary artery spasm)	Ischaemia: acute myocardial ischaemia; reciprocal changes in acute MI
Early repolarization Hyperkalaemia Takotsubo cardiomypathy	Non-ischaemic: LVH/RVH with strain, digoxin effect, hypokalaemia, mitral valve prolapse,
Brugada syndrome	CNS disease e.g. SAH