THE ESSENTIAL 'HOW TO..., WHEN TO...' GUIDE FOR CLINICIANS

OXFORD HANDBOOK OF CLINICAL AND LABORATORY INVESTIGATION

EDITED BY Drew Provan

Provides both a patient-centred and specialty-centred approach to investigation of symptoms and signs, with advice on all relevant tests and the pitfalls of interpreting results

Thoroughly revised, with latest investigations and tests added

Cross-referenced with the Oxford Handbook of Clinical Medicine for more detailed clinical management advice

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Oxford Handbook of Clinical and Laboratory Investigation

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Oxford Handbook of Clinical and Laboratory Investigation

Fourth Edition

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To Richard and Fraser.

Foreword

This book fills an important gap in the market, being a comprehensive guide to the requesting and interpretation of a wide range of diagnostic tests. The authors have crammed a huge amount of information into a relatively small volume. Its size, scope, and relevance mean that it is likely to be used daily as a quick reference and aide-memoire. This fourth edition, which has been entirely updated, covers conditions from the very common, such as nausea and joint pain, to those seen less often. The fact that it is written by experienced clinicians, including trainees, is evident from its practical approach and focus on the patient.

This book highlights the importance, often forgotten, of diagnostic tests in almost all patient care pathways. Its use will ensure that the right investigations are done first time, reducing unnecessary testing and enabling faster and more accurate diagnosis. I am particularly pleased that it contains a section on collecting specimens and how to avoid laboratory errors.

No medical student or junior doctor should be without this book (it is ideal for revision); in fact, any doctor at any stage of their career will find it useful. The appropriate requesting and interpretation of clinical and laboratory investigations is vital for maximizing the value of healthcare and improving the quality of care for patients.

Suzy Lishman
President of The Royal College of Pathologists
2018

Preface to the fourth edition

Six years have elapsed since the third edition of this book was published and during that time there have been advances in investigative techniques, both laboratory-based and clinical. My own specialty, haematology, has seen refinements in diagnostic tests for conditions such as leukaemias and lymphomas, but there have also been developments in the red cell and clotting arenas. My colleagues in other clinical specialties have also enjoyed advances within their own disciplines, and in order to make the book truly contemporary, we have had to update all sections of the book bringing in all of these new techniques.

As before, I have had the privilege to work with leaders in all branches of medicine who have given up their time to update their chapters, bringing them right up-to-date, and I am immensely grateful to them.

I am also indebted to Oxford University Press for their tireless work on this Oxford Handbook which has been used by clinicians worldwide for 14 years. It has grown from 600 pages to almost 1000 in that time! If this small book has helped in the diagnosis of patients, then I feel we have achieved our task. Special thanks go to Michael Hawkes, Elizabeth Reeve, and many others who have helped bring this book to publication.

Being an edited text, I take responsibility for errors or omissions in the book and welcome any comments readers may have. As ever, this book is meant to be used at the bedside and in the clinic, and its usability relies on input from readers. Please contact me at drewprovan@mac.com if you have any suggestions or spot any errors in the book.

Drew Provan
2018

Preface to the first edition

With the increasing complexity of modern medicine, we now have literally thousands of possible investigative techniques at our disposal. We are able to examine our patient's serum and every other body fluid down to the level of individual nucleotides, as well as being able to perform precise imaging through CT, MRI, and other imaging technologies. The problem we have all faced, especially as senior medical students or junior doctors is: Which test should we use in a given setting? What hazards are associated with the tests? Are there any situations where specific tests should not be used or are likely to produce erroneous results? As medical complexity increases, so too does cost; many assays available today are highly expensive and, wherever possible, we would ideally like to use a test that is cheap, reliable, reproducible, and right for a given situation.

Such knowledge takes many years to acquire and it is a fact of life that senior doctors (who have attained such knowledge) are not usually those who request the investigations. In this small volume, we have attempted to distil all that is known about modern tests, from blood, urine, and other body fluids, along with imaging and molecular tests. The book is divided into two principal parts: the first deals with symptoms and signs in *The patient* section, because that is how patients present. We have tried to cover as many topics as possible, discussing these in some detail and have provided differential diagnoses where possible. We also try to suggest tests that might be of value in determining the cause of the patient's symptom or sign. The second part of the book *Investigations* is specialty-specific and is more relevant once you know roughly what type of disease the patient might have. For example, if the symptom section suggests a likely respiratory cause for the patient's symptoms, then the reader should look to the *Respiratory medicine* chapter in order to determine which tests to carry out or how to interpret the results.

The entire book is written by active clinicians, rather than scientists, since we wanted to provide a strong clinical approach to investigation. We have tried, wherever possible, to cross-refer to the *Oxford Handbook of Clinical Medicine*, Oxford University Press, which provides the clinical detail omitted from this handbook. The symbol ➔ is used to highlight a cross-reference to *OHCM*, in addition to cross-referencing within this book.

We would value feedback from readers since there will doubtless be tests omitted, errors in the text, and many other improvements we could, and will, make in future editions. All contributors will be acknowledged individually in the next edition. We would suggest you e-mail us directly.

Drew Provan
Andrew Krentz
2002

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Symbols and abbreviations

~	approximately
α	alpha
β	beta
δ	delta
γ	gamma
κ	kappa
λ	lambda
→	leading to
	cross-reference
↑	increased
↓	decreased
↔	normal
	website
▶	important
▶▶	very important
>	greater than
≥	equal to or greater than
>>	much greater than
<	less than
≤	equal to or less than
=	equal to
+ve	positive
−ve	negative
°	degree
°C	degree Celsius
1°	primary
2°	secondary
♂	male
♀	female
↑↑	greatly increased
±	plus or minus
2D	two-dimensional
3D	three-dimensional
β-TG	beta-thromboglobulin
γGT	gamma-glutamyl transpeptidase
5HIAA	5-hydroxyindole acetic acid

µg	microgram
µL	microlitre
µmol	micromole
^{99m}Tc	technetium-99m
AA	aortic arch
AAA	abdominal aortic aneurysm
AAFB	acid- and alcohol-fast bacilli
ABG	arterial blood gas
ABO	ABO blood groups
ABPA	allergic bronchopulmonary aspergillosis
AC	air conduction
ACD	anaemia of chronic disease
ACE	angiotensin-converting enyme
ACEI	angiotensin-converting enzyme inhibitor
ACh	acetylcholine
AChE	red cell cholinesterase
AChRAb	acetylcholine receptor antibodies
ACL	anticardiolipin antibody
ACPA	anti-cyclic citrullinated peptide antibodies
ACR	albumin:creatinine ratio
ACS	acute coronary syndrome
ACTH	adrenocorticotrophic hormone
ADA	American Diabetes Association
ADC	apparent diffusion coefficient
ADH	antidiuretic hormone
ADP	adenosine 5-diphosphate
AF	atrial fibrillation
AFP	alpha-fetoprotein
AICD	automatic intracardiac defibrillation device
AIDS	acquired immune deficiency syndrome
AIH	autoimmune hepatitis
AIHA	autoimmune haemolytic anaemia
AIP	autoimmune profile
AKI	acute kidney injury
ALD	adrenoleucodystrophy
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALT	alanine transaminase
AMA	antimitochondrial antibodies
AML	acute myeloid leukaemia

ANA	antinuclear antibodies
ANAE	alpha-naphthyl acetate esterase
ANCA	antineutrophil cytoplasmic antibody
ANNA	anti-neuronal nuclear antibodies
AP	anteroposterior; action potential
APCR	activated protein C resistance
APS	antiphospholipid syndrome
APTR	activated partial thromboplastin time ratio
APTT	activated partial thromboplastin time
APVD	anomalous pulmonary venous drainage
ARB	angiotensin II receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ARMS	amplification refractory mutation system
ASAS	Assessment of SpondyloArthritis International Society
ASCA	antibodies to *Saccharomyces cerevisiae*
ASIS	anterior superior iliac spine
ASMA	anti-smooth muscle antibodies
ASO	anti-streptolysin
ASOT	anti-streptolysin O titre
AST	aspartate transaminase
AT	antithrombin
AT-II	angiotensin II
ATN	acute tubular necrosis
AV	atrioventricular; arteriovenous
AVM	arteriovenous malformation
AVN	avascular necrosis
AVP	arginine vasopressin
AVPD	anomalous pulmonary venous drainage
AXR	abdominal X-ray
AZT	zidovudine
BAEP	brainstem auditory evoked potential
BAER	brainstem auditory evoked response
BAL	bronchoalveolar lavage
BC	bone conduction
BCG	bacillus Calmette–Guérin
bd	*bis die* (twice daily)
bDNA	branched-chain deoxyribonucleic acid
BIPLED	bihemispheric periodic lateralized epileptiform discharge
BIRADS	breast imaging and reporting data system

BJP	Bence–Jones protein
BM	bone marrow
BMI	body mass index
BMT	bone marrow transplant
BOLD	blood oxygen level
BP	blood pressure
bpm	beat per minute
BSAEP	brainstem auditory evoked potential
BSG	British Society of Gastroenterology
BSL	Biosafety level
BW	bronchial washing
C&S	culture and sensitivity
Ca^{2+}	calcium
Ca 19-9	carbohydrate antigen 19-9
Ca-125	cancer antigen 125
CAD	computer-assisted detection
CAH	congenital adrenal hyperplasia
cAMP	cyclic adenosine monophosphate
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
CaSR	calcium-sensing receptor
CBC	complete blood count
CBD	common bile duct
CC	craniocaudal
CCF	congestive cardiac failure
CCK	cholecystokinin
CCP	cyclic citrullinated peptide
CCTA	coronary computed tomography angiography
CCU	coronary care unit
CD	cluster differentiation
CEA	carcinoembryonic antigen
cf.	compare with
CF	complement fixation
CFA	cryptogenic fibrosing alveolitis
CFU	colony-forming unit
CGMS	continuous glucose monitoring systems
CHD	coronary heart disease
Cho	choline
CHr	reticulocyte
CINCA	chronic infantite neurologic, cutaneous and articular syndrome
CJD	Creutzfeldt–Jakob disease

CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl^-	chloride
CLL	chronic lymphocytic/lymphatic leukaemia
CLO	*Campylobacter*-like organism
cm	centimetre
CMAP	compound motor action potential
cmH_2O	centimetre of water
CML	chronic myeloid leukaemia
CMR	cardiovascular magnetic resonance
CMV	cytomegalovirus
C3Nef	C3 nephritic factor
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
COHb	carboxyhaemoglobin
COPD	chronic obstructive pulmonary disease
cP	centipoise
CPAP	continuous positive airway pressure
CPE	carbapenemase-producing *Enterobacteriaceae*
CPK	creatinine phosphokinase
CPPD	calcium pyrophosphate disease
CPS	complex partial seizure
Cr	creatine
CrAg	cryptococcal antigen
CrC	creatinine clearance
CRC	colorectal carcinoma
CREST	calcinosis, Raynaud's syndrome, oesophageal motility dysfunction, sclerodactyly, and telangiectasia
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSU	catheter specimen of urine
CT	computed tomography
CTC	computed tomography colonography
CT-IVP	computed tomography intravenous pyelography
CTLp	cytotoxic T-lymphocyte precursor
CTPA	computed tomography pulmonary angiography
CTU	computed tomography urography

CVA	cerebrovascular accident (stroke)
CVD	cardiovascular disease
CVID	common variable immunodeficiency
CVP	central venous pressure
CVS	cardiovascular system; chorionic villus sampling
CW	continuous wave
CXR	chest X-ray
CyF	cystic fibrosis
DAT	direct antibody test
dB	decibel
DBCE	double contrast barium enema
DCCT	Diabetes Control and Complications Trial
DEC	diethylcarbamazine
DESS	dual-echo steady state
DEXA	dual-energy X-ray absorptiometry
DFa	direct fluorescein-labelled monoclonal antibody
DFA	direct fluorescent antibody
DHEAS	dehydroepiandrosterone sulfate
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIDMOAD	diabetes insipidus, diabetes mellitus, optic atrophy, and deafness
DIF	direct immunofluorescence
DIP	distal interphalangeal joint
DJ	duodenojejunal
DKA	diabetic ketoacidosis
dL	decilitre
DLCO	diffusing lung capacity for carbon monoxide
DM	diabetes mellitus
DMSA	dimercaptosuccinic acid
DNA	deoxyribose nucleic acid
DOAC	direct-acting anticoagulant
DPLD	diffuse parenchymal lung disease
dRVVT	dilute Russell viper venom test
DSA	digital subtraction angiography
ds-DNA	double-stranded DNA
DSI	dimensionless severity index
DTI	diffusion tensor imaging
DTPA	diethylenetriaminepentaacetic acid

DU	duodenal ulcer
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
DXA	dual-energy X-ray absorptiometry
EBB	endobronchial biopsy
EBUS	endobronchial ultrasound
EBV	Epstein–Barr virus
ECG	electrocardiogram
EDC	estimated date of confinement
EDH	extradural haemorrhage
EDTA	ethylenediamine tetra-acetic acid
EEG	electroencephalogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EGPA	eosinophilic granulomatosis with polyangiitis
EIA	enzyme-linked assay
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EMA	endomysial antibody
EMG	electromyogram/electromyography
EMU	early morning urine
ENA	extractable nuclear antigen
EOG	electro-oculography
EP	evoked potential
Epo	erythropoietin
EQA	external quality assurance
ER	evoked response
ERCP	endoscopic retrograde cholangiopancreatography
ERF	established renal failure
ESA	erythropoiesis-stimulating agent
ESR	erythrocyte sedimentation rate
ESS	Epworth sleepiness scale
ETT	endotracheal tube
EUS	endoscopic ultrasound
Fab	antibody fragment
FACS	fluorescence-activated cell sorter
FAP	familial polyposis syndrome
FBC	full blood count
FBHH	familial benign hypocalciuric hypercalcaemia

FCHL	familial combined hyperlipidaemia
FDG	fluorodeoxyglucose
FDP	fibrin degradation product
FeNO	exhaled nitric oxide fraction
FEV	forced expiratory volume
FEV_1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FGF	fibroblast growth factor
FH	familial hypercholesterolaemia
FiO_2	inspired oxygen concentration
FISH	fluorescence *in situ* hybridization
fL	femtolitre
FLAIR	fluid attenuation inversion recovery
fMRI	functional magnetic resonance imaging
FNA	fine-needle aspirate/aspiration
FNH	focal nodular hyperplasia
FOB	faecal occult blood
FPG	fasting plasma glucose
Fr	French
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FT4	free T4
FTA-ABS	fluorescent treponemal antibody absorption
FUO	fever of unknown origin
FVC	flow–volume curve; forced vital capacity
FVL	factor V Leiden
g	gram
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
GAn	general anaesthetic
GBM	glomerular basement membrane
GBS	Guillain–Barré syndrome
GC	gas chromatography
GCA	giant cell arteritis
GC-MS	gas chromatography mass spectrometry
GCS	Glasgow Coma Scale
Gd	gadolinium
GFR	glomerular filtration rate
GGT	gamma glutamyl transpeptidase
GH	growth hormone

GHRH	growth hormone-releasing hormone
GI	gastrointestinal
GIT	gastrointestinal tract
GLC	gas–liquid chromatography
GM-CSF	granulocytic macrophage colony-stimulating factor
GnU	genitourinary
GORD	gastro-oesophageal reflux disease
GPA	granulomatosis with polyangiitis
GPC	gastric parietal cell
G6PD	glucose-6-phosphate dehydrogenase
GPI	glycosyl phosphatidyl inositol
GRA	glucocorticoid remediable aldosteronism
G&S	group and save
GT	glucose tolerance
GTN	glyceryl trinitrate
GTT	glucose tolerance test
GU	gastric ulcer
GvHD	graft-versus-host disease
h	hour
HAART	highly active antiretroviral therapy
HACEK	*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* species
HAV	hepatitis A virus
Hb	haemoglobin
HbA_{1c}	haemoglobin A_{1c}
HbC	haemoglobin C
HbD	haemoglobin D
HbE	haemoglobin E
HbF	fetal haemoglobin
HbH	haemoglobin H
HbO	oxyhaemoglobin
HbS	sickle haemoglobin
HbSC	haemoglobin SC
HBV	hepatitis B virus
HC	haemoglobin content
hCG	human chorionic gonadotrophin
HCO_3^-	bicarbonate
Hct	haematocrit
HCV	hepatitis C virus
HD	Hodgkin's disease

HDFN	haemolytic disease of the fetus and newborn
HDL	high-density lipoprotein
HDN	haemolytic disease of the newborn
HELLP	haemolysis, elevated liver enzymes, and low platelet count
HEMPAS	hereditary erythroblastin multinuclearity with positive acidified serum lysis test
HEV	hepatitis E
HHT	hereditary haemorrhagic telangiectasia
HHV	human herpesvirus
Hib	*Haemophilus influenzae* type B
HIE	hypoxic–ischaemic encephalopathy
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HLH	haemophagocytic lymphohistiocytosis syndrome
HMPAO	hexamethyl-propylene-amine-oxime
HMSN	hereditary motor sensory neuropathy
HNA	heparin neutralizing activity
HNF	hepatic nuclear factor
HNPCC	hereditary non-polyposis colorectal carcinoma
HNPP	hereditary neuropathy with liability to pressure palsies
HONK	hyperosmolar non-ketotic
Hp	haptoglobin
HPA	hybridization protection
HPFH	hereditary persistence of fetal haemoglobin
HPLC	high-performance liquid chromatography
HPOA	hypertrophic pulmonary osteoarthropathy
HPV	human papillomavirus
HRC	hypochromic red cell
HRCT	high-resolution computed tomography
HRP-2	histidine-rich protein 2
HRT	hormone replacement therapy
hsTnI	high-sensitivity troponin I
hsTnT	high-sensitivity troponin T
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
HU	Hounsfield unit
HUS	haemolytic uraemic syndrome
HUVS	hypocomple mentaemic urticarial vasculitis syndrome
Hz	hertz
IABP	intra-aortic balloon pump

IAT	indirect antiglobulin test
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICA	islet cell antibodies
ICD	internal cardioverter–defibrillator
ICM	insertable cardiac monitor
ICP	intracranial pressure
ICPMS	inductively coupled plasma mass spectroscopy
ICU	intensive care unit
IDA	iminodiacetic acid
IDDM	insulin-dependent (type 1) diabetes mellitus
IDMS	isotope dilution mass spectrometry
IEF	isoelectric focusing
IF	intrinsic factor
IFA	intrinsic factor antibodies
IFCC	International Federation of Clinical Chemistry
IFG	impaired fasting glucose
IFT	immunofluorescence test
Ig	immunoglobulin
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IGE	idiopathic generalized epilepsy
IGF	insulin-like growth factor
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assays
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
IIH	intracranial hypertension
IL	interleukin
ILD	interstitial lung disease
ILR	implantable loop recorder
IM	intramuscular
IMN	idiopathic membranous nephritis
INR	international normalized ratio
INR/PT	international normalized ratio/prothrombin time
IPSS	inferior petrosal sinus sampling
IQ	intelligence quotient
ITP	idiopathic thrombocytopenic purpura

ITT	insulin tolerance test
ITU	intensive therapy unit
IU	international unit
IUP	intrauterine pregnancy
IV	intravenous
IVC	inferior vena cava
IVI	intravenous infusion
IVP	intravenous pyelography
IVU	intravenous urogram
JME	juvenile myoclonic epilepsy
JVP	jugular venous pressure; jugular venous pulse
K^+	potassium
kBq	kilobecquerel
KCCT	kaolin cephalin clotting time
KCO	transfer coefficient for carbon monoxide
kDa	kilodalton
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
kPa	kilopascal
KSHV	Kaposi's sarcoma-associated herpesvirus
kU	kilounit
KUB	kidney, ureter, bladder (X-ray)
kV	kilovoltage
L	litre
LA	lactic acidosis
LADA	latent autoimmune diabetes of adults
LAn	local anaesthetic
LAP	leucocyte alkaline phosphatase; left atrial pressure
LAt	left atrial
lb	pound
LC	liver cytosol
LCM	left costal margin
LC-MS/MS	liquid chromatography tandem-mass spectrometry
LC/Q-TOF-MS	liquid chromatography/quadrupole time-of-flight mass spectrometry
LCR	ligase chain reaction
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDST	low-dose dexamethasone suppression test
LEMS	Lambert–Eaton myasthenic syndrome

LFT	liver function test
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LIF	left iliac fossa
LKM	liver–kidney microsomal
LMN	lower motor neurone
LOC	loss of consciousness
LP	lumbar puncture
LPL	lipoprotein lipase
LSCC	lateral semicircular canal
LTOT	long-term oxygen therapy
LUQ	left upper quadrant
LV	left ventricle
LVEDP	left ventricular end-diastolic pressure
LVF	left ventricular failure
m	metre
MAA	macroaggregated albumin
MAG	myelin-associated glycoprotein
MAG3	mercaptoacetyl-triglycine
MAHA	microangiopathic haemolytic anaemia
MAIPA	monoclonal antibody immobilization of platelet antigens
MALDI	matrix-assisted laser desorption/ionization
MALDI-TOF MS	matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MALT	mucosa-associated lymphoid tumour
MAOI	monoamine oxidase inhibitor
MARS	Molecular Absorbance Recirculating System
MBq	megabecquerel
MCH	mean cell haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCP	metacarpophalangeal
M,C&S	microscopy, culture, and sensitivity
MCUG	micturating cystourethrogram
MCV	mean cell volume
MCVm	mutated citrullinated vimentin
MD	myotonic dystrophy
MDMA	methylene dioxymethamphetamine or ecstasy
MDR	multi-drug-resistant
MDRD	Modification of Diet in Renal Disease
MDR-TB	multi-drug-resistant tuberculosis

MDS	myelodysplastic syndrome
MELAS	mitochondrial myopathy, lactic acidosis, and stroke-like episodes
MEN	multiple endocrine neoplasia
MEP	motor evoked potential
mEq	milliequivalent
MERRF	myoclonic epilepsy and ragged red fibres
MERS-CoV	Middle East respiratory syndrome coronavirus
MetHb	methaemoglobin
mg	milligram
Mg^{2+}	magnesium
MG	myasthenia gravis
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MHz	megahertz
MI	myocardial infarction
MIBG	iodine-131-meta-iodobenzylguanide
MIC	minimum inhibitory concentration
min	minute
m-In	myo-inositol
mIU	milli-international unit
mL	millilitre
MLC	mixed lymphocyte culture
MLO	mediolateral oblique
mm	millimetre
mmHg	millimetre of mercury
M-mode	motion-mode
mmol	millimole
MND	motor neurone disease
MoAb	monoclonal antibody
MODY	maturity-onset diabetes of the young
mOsmol	milliosmole
MP	metacarpophalyngeal
mPA	millipascal
MPD	myeloproliferative disease
MPHR	max predicted heart rate
MPI	myocardial perfusion imaging
MPO	myeloperoxidase
MPV	mean platelet volume
MR	magnetic resonance

MRA	magnetic resonance angiogram
MRC	Medical Research Council
MRCP	magnetic resonance cholangiopancreatography
MRD	minimal residual disease
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRS	magnetic resonance spectroscopy
MRSA	meticillin-resistant *Staphylococcus aureus*
MRV	magnetic resonance venography
ms	millisecond
MS	multiple sclerosis
MSD	mean sac diameter
MSU	midstream urine
mSv	millisievert
MTP	metatarsophalangeal
mU	milliunit
MUGA	multigated radionuclide angiography
MUP	motor unit potential
MuSK	muscle-specific kinase
mV	millivolt
Na^+	sodium
NAA	*N*-acetyl-aspartate
NAC	*N*-acetylcysteine
NAG	*N*-acetyl-*D*-glucosaminidase
NAP	neutrophil alkaline phosphatase
NASBA	nucleic acid sequence-based amplification
NCS	nerve conduction studies
NCSE	non-convulsive status epilepticus
NEC	necrotizing enterocolitis
NET	neuroendocrine tumour
ng	nanogram
NH_3	ammonia
NH_4^+	ammonium
NHL	non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NK	natural killer
nm	nanometre
nmol	nanomole

NMS	neuroleptic malignant syndrome
NO	nitric oxide
NOGG	National Osteoporosis Guideline Group
NPA	nasopharyngeal aspirate
NPH	normal pressure hydrocephalus
NPSA	National Patient Safety Agency
NREM	non-rapid eye movement
NSAID	non-steroidal anti-inflammatory drug
NSF	nephrogenic systemic fibrosis
NSTEMI	non-ST-elevation myocardial infarction
O_2	oxygen
OA	osteoarthritis
Oc	calculated osmolality
OCB	oligoclonal band
OCP	oral contraceptive pill
OGD	oesophagogastroduodenoscopy
OGTT	oral glucose tolerance test
OHCM	*Oxford Handbook of Clinical Medicine*
Om	measured osmolality
OMIM	Online Mendelian Inheritance in Man
OSA	obstructive sleep apnoea
OTC	over the counter
PA	pernicious anaemia
P-A	posteroanterior
PABA	para-amino benzoic acid; *N*-benzoyl-*L*-tyrosol *p*-aminobenzoic acid
P_aCO_2	partial pressure of carbon dioxide in arterial blood
PACS	picture archiving and communication systems
PAD	peripheral arterial disease
PAN	polyarteritis nodosa
p-ANCA	perinuclear antineutrophil cytoplasmic antibody
P_aO_2	arterial oxygen tension
PAS	periodic acid–Schiff
PB	peripheral blood
PBC	primary biliary cirrhosis
PC	protein C; provocation concentration
PCH	paroxysmal cold haemoglobinuria
PCI	percutaneous coronary intervention
PCNA	proliferating cell nuclear antigen
PCO_2	partial passure of carbon dioxide

PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PCrR	protein:creatinine ratio
PCT	procalcitonin
PCV	packed cell volume
PD	Parkinson's disease
PDW	platelet distribution width
PE	pulmonary embolism/embolus
PEFR	peak expiratory flow rate
PEG	percutaneous endoscopic gastrostomy
PET	positron emission tomography
PFR	peak flow rate
pg	picogram
PICC	peripherally inserted central catheter
PIFT	platelet immunofluorescence test
PIP	proximal interphalangeal
PK	pyruvate kinase
PkS	Parkinson's syndrome
PLA-2	phospholipase A2
PLED	periodic lateralized epileptiform discharge
PLMD	paroxysmal leg movement disorder
PmA	pulmonary artery
PMA	paramethoxymethamphetamine
PMF	progressive massive fibrosis
PMLE	progressive multifocal leukoencephalopathy
PNH	paroxysmal nocturnal haemoglobinuria
PNS	peripheral nervous system
PO	*per os* (by mouth)
PO_2	partial pressure of oxygen
PO_4^{3-}	phosphate
POTS	postural orthostatic tachycardia syndrome
PP	pancreatic polypeptide
ppb	parts per billion
PPD	purified protein derivative
PR	per rectum
PR3	proteinase 3
PRA	plasma renin activity
PrC	provocation concentration
PRL	prolactin
PRV	polycythaemia rubra vera

PS	protein S
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PT	prothrombin time
PTA	percutaneous transluminal angioplasty
PTC	percutaneous transhepatic cholangiogram
PTH	parathyroid hormone
PTR	prothrombin ratio
PTTK	partial thromboplastin time with kaolin
PUO	pyrexia of unknown origin
PV	plasma volume
PVA	polyvinyl alcohol
PvC	provocation concentration
PVNS	pigmented villonodular synovitis
PW	pulsed wave
PWI	perfusion-weighted imaging
PxCT	proximal convoluted tubule
qds	*quarter die sumendus* (four times daily)
RA	refractory anaemia
RAPA	rheumatoid arthritis particle agglutination test
RAS	renal artery stenosis
RAST	radioallergosorbent test
RAt	right atrial/atrium
RBC	red blood cell
RBP	retinol-binding protein
RCC	red cell count
RDT	rapid diagnostic test
RDW	red cell distribution width
REM	rapid eye movement
RES	reticuloendothelial system
Ret-He	reticulocyte haemoglobin content
RF	rheumatoid factor
RFLP	restriction fragment length polymorphism
Rh	rhesus
RhA	rheumatoid arthritis
RhMK	Rhesus monkey kidney
RIA	radioimmunoassay
RiCoF	Ristocetin Cofactor
RID	radial immunodiffusion
RIF	right iliac fossa

RIPA	ristocetin-induced platelet aggregation
RIS	radiology information system
RNP	ribonucleoprotein
RNV	radionuclide ventriculography
RPR	rapid plasma reagin
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
rTMS	repetitive transcranial magnetic stimulation
RUQ	right upper quadrant
RV	right ventricle; residual volume
s	second
SAA	serum amyloid A
SAAG	serum ascites albumin gradient
SAH	subarachnoid haemorrhage
SaO_2	arterial oxygen saturation
SARS	severe acute respiratory syndrome
SB	Sudan black
SBE	subacute bacterial endocarditis
SBO	small bowel obstruction
SBP	spontaneous bacterial peritonitis
sbt	serum bactericidal test
SC	subcutaneous
SCC	squamous cell carcinoma
SCID	severe combined immunodeficiency
SCLC	small-cell lung cancer
SDH	subdural haemorrhage
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SeHCAT	^{75}selenium homotaurocholate
SG	specific gravity
SGLT2	sodium–glucose cotransporter 2
SHBG	sex hormone-binding globulin
SI	Système International
SIADH	syndrome of inappropriate antidiuretic hormone
SLA	soluble liver antigen
SLE	systemic lupus erythematosus
SMA	smooth muscle antibody
SNAP	sensory nerve action potential
SO_4^{2-}	sulfate
SOB	shortness of breath
SOD	sphincter of Oddi dysfunction

SOL	space-occupying lesion
SPECT	single photon emission computed tomography
SpO_2	oxygen saturation
SSFP	steady-state free precession
SSP	single strand polymorphism
SSPE	subacute sclerosing panencephalitis
SSR	somatostatin receptor
STD	sexually transmitted disease
STEMI	ST-elevation myocardial infarction
sTfR	serum transferrin receptor
STfR	soluble transferrin receptor assay
STIR	short tau inversion recovery
SUV	standardized uptake value
SVC	superior vena cava
SWS	slow wave sleep
SXR	skull X-ray
T	testa
T1W	T1-weighted
T2W	T2-weighted
TA	temporal arteritis
TACO	transfusion-associated circulatory overload
TB	tuberculosis
TBLB	transbronchial lung biopsy
TBNA	transbronchial needle aspiration
TCR	T-cell receptor
TCT	thrombin clotting time
tds	*ter die sumendus* (three times daily)
TE	echo time
TfR	transferrin receptor
TFT	thyroid function test
Tg	thyroglobulin
TG	triglyceride
THR	total hip replacement
TIA	transient ischaemic attack
TIBC	total iron binding capacity
TIPS	transjugular intrahepatic portosystemic shunt
TLC	thin-layer chromatography; total lung capacity
TLCO	transfer factor for carbon monoxide
TMA	thrombotic microangiopathy; transcription-mediated amplification

TMS	transcranial magnetic stimulation
TN	trigeminal neuralgia
TnI	troponin I
TnT	troponin T
TOE	transoesophageal echocardiography
tPA	tissue plasminogen activator
TPHA	*Treponema pallidum* haemagglutination assay
TPN	total parenteral nutrition
TPO	thyroid peroxidase
TR	repetition time
TRALI	transfusion-related acute lung injury
TRAP	tartrate-resistant acid phosphatase
TRH	thyrotropin-releasing hormone
tRNA	transfer ribonucleic acid
TRP	tubular reabsorption of phosphate
TSE	transmissible spongiform encephalopathy
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
tTG	tissue transglutaminase
TTP	thrombotic thrombocytopenic purpura
U	unit
UCTD	undifferentiated connective tissue disease
U&E	urea and electrolytes
UFC	urinary free cortisol
UFE	uterine fibroid embolization
UK	United Kingdom
UMN	upper motor neurone
URTI	upper respiratory tract infection
US	ultrasound
USA	United States
USS	ultrasound scan
UTI	urinary tract infection
UV	ultraviolet
VATS	video-assisted thoracoscopic surgery
VC	vital capacity
vCJD	variant Creutzfeldt–Jakob disease
VDRL	Venereal Disease Research Laboratory
VEP	visual evoked potential
VHF	viral haemorrhagic fever
VHL	von Hippel–Lindau

VIP	vasoactive intestinal peptide
VLCFA	very long-chain fatty acid
VLDL	very low-density lipoprotein
VMA	vanillylmandelic acid
VO_2	oxygen uptake
VO_{2max}	maximum oxygen uptake
VP	vasoactive peptide
V/Q	ventilation/perfusion
VRE	vancomycin-resistant *Enterococcus*
VSD	ventricular septal defect
VTE	venous thromboembolism
vWD	von Willebrand disease
vWF Ag	von Willebrand factor antigen
WBC	white blood count/cells
WCE	wireless capsule endoscopy
WHO	World Health Organization
w/v	weight by volume
XDP	cross-linked fibrin degradation product
XDR-TB	extensively drug-resistant tuberculosis
XLA	X-linked agammaglobulinaemia
ZN	Ziehl–Neelsen
ZPP	zinc protoporphyrin

Approach to investigations

Why do tests?

Patients seldom present to their doctors with *diagnoses*—rather, they have symptoms or signs. The major challenge of medicine is being able to talk to the patient and obtain a history, then carry out a physical examination looking for pointers to their likely underlying problem. Our elders and, some would argue, betters in medicine had fewer tests available to them than we have today, and their diagnoses were often made solely from the history and examination. Of course, they would claim that their clinical acumen and skills were greater than ours, and that we rely too heavily on the huge armoury of laboratory and other investigations available today. This, in part, is probably true, but we cannot ignore the fact that advances in science and technology have spawned a bewildering array of very useful and sophisticated tests that help us to confirm our diagnostic suspicions.

By 'test' we mean the measurement of a component of blood, marrow, or other body fluid or physiological parameter to determine whether the patient's value falls within or outside the normal range, either suggesting the diagnosis or, in some cases, actually making the diagnosis for us.

Factors affecting variable parameters in health

Many measurable body constituents vary throughout life. For example, a newborn baby has an extremely high haemoglobin concentration, which falls after delivery. This is completely normal and is *physiological*, rather than *pathological*. A haemoglobin level this high in an adult would be pathological, since it is far outside the normal range for the adult population.

Factors affecting measurable variables

- Age.
- Sex.
- Ethnicity.
- Altitude.
- Build.
- Physiological conditions (e.g. at rest, after exercise, standing, lying).
- Sampling methods (e.g. with or without using a tourniquet).
- Storage and age of sample.
- Container used, e.g. for blood sample, as well as anticoagulant.
- Method of analysis.

Reference ranges (normal values)

These are published for most measurable components of blood and other tissue, and we have included the normal ranges for most blood and cerebrospinal fluid (CSF) analytes at the end of the book.

What makes a test useful?

A really good test, and one that would make us appear to be outstanding doctors, would be one that would *always* be positive in the presence of a disease and would be *totally* specific for that disease alone; such a test would never be positive in patients who did not have the disorder. What we mean is that what we are looking for are *sensitive* tests that are *specific* for a given disease. Sadly, most tests are neither 100% sensitive nor 100% specific, but some do come very close.

How to use tests and the laboratory

Rather than request tests in a shotgun or knee-jerk fashion where every box on a request form is ticked, it is far better to use the laboratory selectively. Even with the major advances in automation where tests are batched and are cheaper, the hospital budget is finite and sloppy requesting should be discouraged.

Outline your differential diagnoses: what are the likeliest diseases, given the patient's history, examination findings, and population from which the patient come?

Decide which test(s) will help you make the diagnosis: request these and review the diagnosis in the light of the test results. Review the patient and arrange further investigations as necessary.

The downside of tests

It is important to remember that tests may often give 'normal' results, even in the presence of disease. For example, a normal electrocardiogram (ECG) in the presence of chest pain does *not* exclude the occurrence of myocardial infarction with 100% certainty. Conversely, the presence of an abnormality does not necessarily imply that a disease is present. This, of course, is where clinical experience comes into its own—the more experienced clinician will be able to balance the likelihood of disease with the results available, even if some of the test results give unexpected answers.

Sensitivity and specificity	
Sensitivity	% of patients with the disease and in whom the test is positive
Specificity	% of people without the disease and in whom the test is negative

Quick-fix clinical experience

This simply does not exist. Talking to patients and examining them for physical signs and assimilating knowledge gained in medical school are absolute requirements for attainment of sound clinical judgement. Those students and doctors who work from books alone do not survive effectively at the coal face! It is a constant source of irritation to medical students and junior doctors, when a senior doctor asks for the results of an investigation on the ward round and you find this test is the one that clinches the diagnosis. How *do* they do it? Like appreciating good wine—they develop a nose for it. You can learn a great deal by watching your registrar or consultant make decisions. This forms the basis of your *own* clinical experience.

Laboratory errors and how to avoid them

It is a fact of life that the sophisticated automated analysers in current use are not 100% accurate 100% of the time, but they come pretty close. In order to keep errors to a minimum, precautions need to be taken when sampling biological material, e.g. blood.

Minimizing spurious results using blood samples

- Use correct bottle.
- Fill to line (if anticoagulant used). This is less of a worry when vacuum sample bottles are used since these should take in exactly the correct amount of blood, ensuring the correct blood:anticoagulant ratio. This is critical for coagulation tests.
- Try to get the sample to the laboratory as quickly as possible. Blood samples left lying around on warm windowsills, or even overnight at room temperature, will produce bizarre results, e.g. crenated red blood cells (RBCs) and abnormal-looking white blood cells (WBCs) in old EDTA samples.
- Try to avoid rupturing red cells when taking the sample (e.g. using narrow-gauge needle, prolonged time to collect whole sample); otherwise a 'haemolysed' sample will be received by the laboratory. This may cause spurious results for some parameters (e.g. $[K^+]$).
- Remember to mix (not shake) samples containing anticoagulant.

Variations in normal ranges in health

As discussed earlier, most of the normal ranges for blood parameters discussed in this book are for non-pregnant adults. The reason for this is that blood values, e.g. haemoglobin (Hb), red cell count (RCC), are high in the newborn and many full blood count (FBC), coagulation, and other parameters undergo changes in pregnancy.

Part I

The patient

Chapter 1

Symptoms and signs

Abdominal distension

Patients may describe generalized abdominal swelling or localized fullness in a specific area of the abdomen.

In the history enquire specifically about

- Change in bowel habit.
- Weight loss.
- Associated pain.

Generalized swelling

Consider

- Fat.
- Fluid.
- Faeces.
- Flatus.
- Fetus.
- Full bladder.

Ascites

Fluid in the peritoneal cavity. Look for shifting dullness and fluid thrill on percussion, stigmata of chronic liver disease, lymphadenopathy, and oedema, and assess the jugular venous pressure (JVP).

Causes

- Malignancy.
- Cirrhosis/portal hypertension.
- Hypoproteinaemia.
- Right heart failure.

Investigations

- Urea and electrolytes (U&Es).
- Liver function tests (LFTs).
- Serum albumin.
- Ascitic tap for cytology, and microscopy, culture, and sensitivity (M,C&S).
- Serum-ascites albumin gradient.
- Ultrasound scan (USS) of the abdomen.

(See Fig. 1.1.)

Flatus

Gaseous distension. Need to exclude bowel obstruction. Assess for colicky abdominal pain, bowel habit, flatus, and vomiting. Look for resonant distension on percussion, altered or absent bowel sounds, and focal tenderness with rebound and guarding. Always check for herniae and perform a per rectum (PR) examination in suspected obstruction.

Causes

- *Intraluminal*: faecal impaction, gallstone ileus.
- *Luminal*: inflammatory stricture (e.g. Crohn's), tumour, abscess.
- *Extraluminal*: herniae, adhesions, pelvic mass, lymphadenopathy, volvulus, intussusception.

- *Paralytic ileus*: drug-induced, electrolyte disturbances.
- Age-related causes of obstruction.
- *Neonatal*: congenital atresia, imperforate anus, volvulus, Hirschsprung's disease, meconium ileus.
- *Infants*: intussusception, Hirschsprung's, herniae, Meckel's diverticulum.
- *Young/middle-aged adults*: herniae, adhesions, Crohn's.
- *Elderly*: herniae, carcinoma, diverticulitis, faecal impaction.

Investigations

- Full blood count (FBC).
- U&E.
- Abdominal X-ray (AXR) (erect and supine).
- Consider barium enema, barium follow-through, sigmoidoscopy, surgical intervention for complete acute obstruction.

Localized swelling/masses: common causes according to site

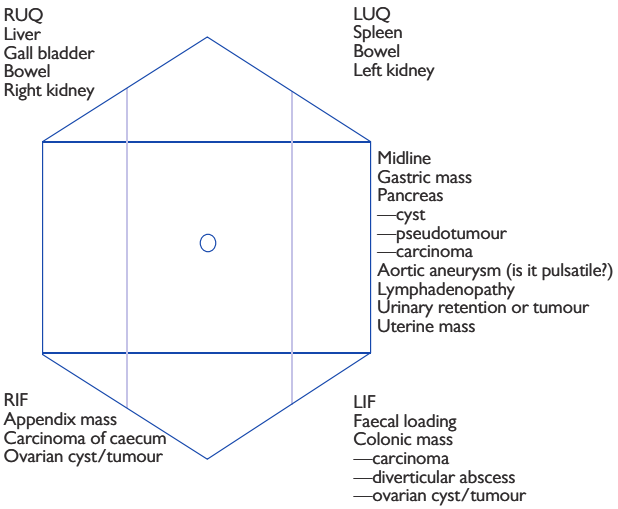


Fig. 1.1 Main causes of abdominal swelling according to site.

Investigate according to site

- Consider USS abdomen and pelvis.
- Computed tomography (CT) scanning.
- Barium studies.
- Intravenous urogram (IVU).

➔ *OHCM* 10e, p. 62, p. 604.

Abdominal pain

Abdominal pain may be acute or chronic. Severe acute pain may indicate a surgical emergency, including perforation, peritonitis, or obstruction. Assess nature and radiation of pain, clinical status of the patient, including fever, tachycardia, and hypotension.

Common causes of abdominal pain according to site

Epigastric pain
Peptic ulcer disease, gastritis or duodenal erosions, cholecystitis, pancreatitis.

Periumbilical pain
Pancreatitis, mesenteric artery ischaemia (older patient with vascular disease).

Right upper quadrant (RUQ) pain
Biliary colic, cholecystitis, hepatitis, peptic ulcer.

Left upper quadrant (LUQ) pain
Splenic, peptic ulcer.

Loin pain
Renal colic (colicky radiating loin → groin), pyelonephritis, renal pathology.

Left iliac fossa (LIF) pain
Constipation, diverticular disease, irritable bowel syndrome (IBS), pelvic referred pain, inflammatory bowel disease (IBD).

Right iliac fossa (RIF) pain
Appendicitis, pelvic referred pain, IBD (e.g. Crohn's of terminal ileum).

Suprapubic pain
Urinary tract infection (UTI), cystitis, salpingitis.

Generalized pain
Gastroenteritis, irritable bowel, constipation, generalized peritonitis.

Pitfalls

- *Metabolic causes*, e.g. diabetic ketoacidosis (DKA), hypercalcaemia, Addison's disease, porphyria, lead poisoning.
- *Atypical referred pain*, e.g. myocardial infarction (MI), pneumonia.

Investigations

- FBC.
- U&E, e.g. deranged electrolytes following vomiting, diarrhoea, or bowel obstruction.
- Plasma glucose.
- Serum amylase (↑ in pancreatitis and bowel obstruction).
- Urinalysis and midstream urine (MSU), e.g. haematuria, proteinuria, glucose.
- LFTs (consider obstructive vs hepatitic picture).
- Plain AXR (erect and supine to assess for perforation and bowel obstruction).
- Kidney, ureter, bladder X-ray (KUB) for renal tract calculi.
- USS abdomen, particularly for biliary tract, gall bladder, and renal tract.
- IVU to assess for renal tract calculi/pathology.

➔ *OHCM* 10e, p. 30, p. 57, p. 609.

Alteration of behaviour

This is usually reported by a relative or friend, rather than by the patient. Often the patient will have little or no insight into the disease and taking a history can be difficult. In addition to a full general and neurological physical examination, a mental state examination is required.

Find out if this is the first episode of altered behaviour or if the episodes are recurrent. Is there a gradual change in behaviour (and personality) over time?

Acute delirium

Causes

- Sepsis (common).
- Acute intracranial event, e.g. haemorrhage.
- Metabolic disturbance, e.g. uraemia, hypercalcaemia (common).
- Intracerebral tumour (including meningioma).
- Drugs—especially interactions in the elderly.
- Alcohol (and withdrawal syndrome).
- Hypoxia (common).
- Hypoglycaemia (iatrogenic in diabetic patients receiving insulin treatment or oral insulin secretagogues, or insulinoma and other causes).

Dementia

- Alzheimer's (common), Pick's (rare).
- Vascular, e.g. multi-infarct.
- Huntington's chorea.
- Vitamin B_{12} deficiency (severe).
- Hypothyroidism (severe).
- Wilson's disease.
- Alcoholism.
- Normal pressure hydrocephalus.

Note: 'frontal lobe syndrome' from space-occupying lesion (SOL), e.g. meningioma. Presents with disinhibition, impaired social functioning, primitive reflexes, e.g. grasp reflex.

Anxiety states

Usually psychogenic, but consider organic possibilities such as

- Phaeochromocytoma (rare).
- Hyperthyroidism (common).
- Paroxysmal atrial tachycardia (fairly common).
- Alcohol withdrawal (usually history of excessive alcohol intake).

Psychosis

- Schizophrenia.
- Bipolar disorder or pseudo-dementia in:
  - Systemic lupus erythematosus (SLE).
  - Cushing's syndrome.
  - Multiple sclerosis (MS).
  - Thyrotoxicosis ('apathetic' thyrotoxicosis in the elderly).

Temporal lobe epilepsy

- Temporary disturbance of content of consciousness.

Investigations: guided by history and examination

- U&E.
- Glucose (in non-diabetics, take fasting venous plasma in a fluoride oxalate tube with simultaneous serum or plasma for insulin concentration, e.g. suspected insulinoma).
- Chest X-ray (CXR).
- LFTs.
- Thyroid function tests (TFTs).
- FBC.
- Erythrocyte sedimentation rate (ESR).
- Urinalysis (protein, nitrites, glucose).
- Cranial CT scan.
- Serum vitamin B_{12}.
- Arterial blood gases (ABGs) ± carboxyhaemoglobin (COHb).
- Blood cultures.

Consider

- Syphilis serology.
- Human immunodeficiency virus (HIV) test.
- Urine drug screen (➔ Chapter 11).
- Blood ethanol level (may be low in withdrawal state).
- Electroencephalogram (EEG).
- 24h electrocardiogram (ECG).
- Sleep study.

Alteration in bowel habit

A change in bowel habit in an adult should always alert you to the possibility of bowel cancer. Ask about associated features—PR bleeding, tenesmus, weight loss, mucus, abdominal pain, or bloating.

Has the patient started any new medications, including 'over the counter'? Look for signs of systemic disease.

Consider

- Carcinoma of the colon.
- Diverticular disease.
- IBS.
- Constipation with overflow diarrhoea.
- All of the above may present with alternating diarrhoea and constipation.

Investigations

- Digital rectal examination.
- Proctoscopy.
- Sigmoidoscopy (rigid/flexible).
- Colonoscopy.
- Barium enema.
- CT colonography.

➔ Diarrhoea (pp. 32–3), ➔ Constipation (pp. 29–30), ➔ Incontinence: faecal (p. 60).

Anaemia

Reduced haemoglobin (Hb), no specific cause implied (and *not a diagnosis in itself, so don't be complacent*): ♂ <13.5g/dL, ♀ <11.5g/dL. Often associated with non-specific symptoms such as fatigue, poor concentration, shortness of breath, and dizziness. Older patients may experience palpitations and exacerbation of angina, congestive cardiac failure (CCF), or claudication.

Signs

Pallor of conjunctivae and skin creases, nail pallor and koilonychia (spoon-shaped nails, very rare finding in severe chronic iron deficiency), angular cheilitis, and glossitis. Most of these signs are unreliable and it is difficult to gauge anaemia from skin signs alone.

Causes

(See Table 1.1.)

Two common approaches to assess anaemia are:

1. *Red cell dynamics*:
   - ↑ Red blood cell (RBC) loss/breakdown, e.g. haemolysis (congenital or acquired) or bleeding.
   - ↓ RBC production, e.g. vitamin/mineral deficiency, marrow suppression/infiltration, myelodysplasia, Hb disorders (e.g. thalassaemia), chronic disease, renal failure.
2. *Red cell indices*:

Investigations

FBC and film

Assessment of RBC indices helps direct investigation as above.

Table 1.1 Some causes of anaemia based on the MCV

Microcytic/hypochromic	↓ MCV, ↓ MCHC, e.g. Iron deficiency Thalassaemia Anaemia of chronic disease
Macrocytic	↑ MCV Reticulocytosis (polychromasia on blood film) B_{12} or folate deficiency Chronic liver disease Hypothyroidism Alcohol Myelodysplasia
Normocytic, normochromic	↔ MCV and MCHC Anaemia of chronic disease, e.g. • Chronic infection • Inflammation Inflammatory disease or malignancy Acute blood loss Renal failure Myeloma

MCHC, mean corpuscular haemoglobin concentration; MCV, mean cell volume.

Microcytic

- Check iron stores (ferritin or soluble transferrin receptor assay). *Note*: ferritin is ↑ in acute inflammation and may be misleading. Iron/total iron binding capacity (TIBC) no longer used for assessment of iron deficiency (➔ Assessment of iron status, pp. 244–7).
- Consider thalassaemia screening if not iron-deficient (i.e. ↓ MCV, ↔ ferritin).
- If iron-deficient, assess dietary history (vegetarians) and look for risk factors for blood loss and ↑ demands.
- Premenopausal women: assess menstrual losses.
- Pregnancy/infants/adolescence: consider physiological (↑ requirements).
- All others: look for source of blood loss. The gastrointestinal (GI) tract is the commonest source. Consider oesophagogastroduodenoscopy (OGD) and/or colonoscopy if clinically indicated by symptoms and barium studies.

Macrocytic

- Reticulocyte count.
- Serum B_{12} and red cell folate levels.
- If folate-deficient: assess dietary history and physiological requirements.
- If B_{12}-deficient: rarely dietary cause alone, usually an associated pathology. Pernicious anaemia (PA) is the commonest cause—check parietal cell antibodies (90% of patients with PA are +ve, but seen in other causes of gastric atrophy, especially in older individuals) and/or intrinsic factor antibodies (+ve in only 50% with PA, but specific). Consider ileal disease and malabsorption.
- LFTs.
- Thyroid function.

Normocytic

- Blood film.
- ESR.
- Renal function.
- Consider myeloma screen in older adults (immunoglobulins (Igs), protein electrophoresis, urine Bence–Jones protein (BJP)). Skeletal survey of value if paraprotein or BJP.
- Autoimmune screen to exclude connective tissue disease.

Haemolysis screen

- FBC, mean cell volume (MCV) (↑ due to reticulocytosis—these are larger than RBCs).
- Blood film (spherocytes, polychromasia, bite cells, and red cell fragmentation).
- Reticulocyte count.
- Serum bilirubin and serum lactate dehydrogenase (LDH).
- Haptoglobins (absent in haemolysis).
- Direct antibody test (DAT) (old term is direct Coombs' test).

Consider

- Congenital haemolytic anaemias: membrane defects, enzyme deficiencies (e.g. glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase).
- Disseminated intravascular coagulation (DIC)/microangiopathic haemolysis—DIC screen.

Anaphylaxis

Defined as a systemic reaction (local oral angio-oedema is *not* anaphylaxis), with any or all of the following:

- Stridor (laryngeal obstruction).
- Wheeze (bronchospasm).
- Generalized urticaria and/or angio-oedema.
- Hypotension ± loss of consciousness.
- Abdominal pain/cramps, vomiting, and diarrhoea.

Note: not all patients have urticaria or rash—only 50% will do so.

Differentiate IgE-mediated reactions (*anaphylaxis*) from non-IgE-mediated reactions (*anaphylactoid*)—due to direct mast cell degranulation).

Angio-oedema

Angio-oedema is deep tissue swelling which is non-itchy. May be premonitory tingling. May occur with or without urticaria. Caused by bradykinin, not histamine.

Causes

- As for urticaria; also hereditary angioedema (rare).
- Also think of drugs—these are the commonest cause:
  - Angiotensin-converting enzyme (ACE) inhibitors (ACEIs) (elevated bradykinin levels due to inhibition of breakdown).
  - Angiotensin II (AT-II) receptor antagonists.
  - Statins.
  - Proton pump inhibitors.
  - Non-steroidal anti-inflammatory drugs (NSAIDs).

May also be seen in patients with autoimmune disease, such as lupus and rheumatoid arthritis (RhA) (antibodies against C1q), and in older patients in association with paraproteins (myeloma, lymphoma).

Angio-oedema *with* urticaria is *not* due to hereditary angio-oedema.

Investigations

- Check drug history first! If suspect drugs, then stop drugs and wait! If no drugs, then investigate.

Angio-oedema WITH urticaria

- Investigate as for urticaria.

Angio-oedema WITHOUT urticaria

- Complement C3 and C4.
- If C4 low, check C1 esterase inhibitor (immunochemical and functional).
- Serum Igs and electrophoresis.
- Autoantibody screen.
- FBC and ESR.
- Thyroid function.
- Liver function.

Anorexia

This describes a loss of appetite for food and is associated with a wide range of disorders. In fact, anorexia is a fairly common consequence of underlying disease and represents general undernourishment. Anorexia per se is associated with ↑ morbidity, especially when present in patients undergoing surgery; post-operative infection is commoner, as is prolongation of the hospital stay.

The extent to which it will be investigated depends on the general status of the patient and the presence and duration of any symptoms or signs. Clinical judgement will help!

Causes

- Anorexia nervosa.
- Depressive illness.
- Stress.
- Cancers: any, including carcinoma of the stomach or oesophagus, metastatic, leukaemia, or lymphoma.
- Drugs, including chemotherapy.
- Radiotherapy.
- Renal failure.
- Hypercalcaemia.
- Infections.
- Cigarette smoking.

Investigations

- Full history and examination.
- FBC—looking for anaemia or non-specific changes seen in underlying disease.
- ESR—may be elevated in inflammatory disorders.
- U&E.
- LFTs.
- Serum calcium (Ca^{2+}).
- CXR (e.g. lung cancer, tuberculosis (TB), etc.).
- Cultures of blood, sputum, urine, stool if pyrexial and/or localizing symptoms or signs.

Anuria

Anuria denotes absent urine production. Oliguria (<400mL urine/24h) is commoner than anuria. A catheter must be passed to confirm an empty bladder.

Causes

- Urinary retention—prostatic hypertrophy; pelvic mass; drugs, e.g. tricyclic antidepressants; spinal cord lesions.
- Blocked indwelling urinary catheter.
- Obstruction of the ureters—tumour, stone, sloughed papillae (bilateral).
- Intrinsic renal failure—acute glomerulonephritis, acute interstitial nephritis, acute tubular necrosis (ATN), rhabdomyolysis.
- Pre-renal failure—dehydration, septic shock, cardiogenic shock.

An urgent USS of the renal tract must be performed and any physical obstruction relieved as quickly as possible, either directly (urethral catheter) or indirectly (nephrostomy).

►► *Renal function and serum electrolytes must be measured without delay.*

Further tests as clinically indicated

- FBC.
- Blood cultures.
- ABGs.
- Uric acid.
- Autoimmune profile.
- ESR.
- Creatine kinase (CK).
- Prostate-specific antigen (PSA) (prostatic carcinoma).
- Serum Ca^{2+} and phosphate (PO_4^{3-}).
- 12-lead ECG.
- CXR.
- Central venous pressure (CVP) measurement via central line (to guide intravenous (IV) fluids).
- MSU (UTI).
- Urine microscopy (for casts).
- Urine osmolality, sodium, creatinine, urea concentrations.
- IVU (➔ Radiology of the urinary tract, pp. 808–11).
- Urinary stone analysis, if available.
- CT pelvis.
- Renal biopsy (if intrinsic renal disease suspected, normal-sized kidneys).

➔ *OHCM* 10e, p. 81, p. 293.

Ataxia

Ataxia is an impaired ability to coordinate limb movements. There must be no motor paresis (e.g. monoparesis) or involuntary movements (e.g. the characteristic cogwheel tremor in Parkinson's disease (PD) is not ataxia).

Ataxia may be

- Cerebellar.
- Vestibular.
- Sensory.

Note: many forms of ataxia are hereditary (but are uncommon).

Hereditary causes

- Friedreich's ataxia.
- Ataxia telangiectasia.
- Spinocerebellar ataxia.
- Corticocerebellar atrophy.
- Olivopontocerebellar atrophy.
- Hereditary spastic paraplegia.
- Xeroderma pigmentosa.

Investigations

- Family studies.
- Genetic analysis (discuss with the regional genetics laboratory—counselling may be required).

Vestibular ataxia

- Acute alcohol intoxication.
- Labyrinthitis.

Sensory ataxia

- Loss of proprioception—peripheral neuropathy, dorsal column disease.
- Visual disturbance.

Investigations

- Venous plasma glucose (diabetic neuropathy).
- Serum vitamin B_{12} (subacute combined degeneration of the cord—rare, but serious).
- LFTs.
- Cryoglobulins.

Cerebellar ataxia

- Demyelinating diseases, e.g. MS.
- Cerebellar infarct or haemorrhage.
- Alcoholic cerebellar degeneration.
- Cerebellar tumour—1° in children, metastases in adults. *Note*: von Hippel–Lindau (VHL) disease (➔ *OHCM* 10e, Chapter 19).
- Nutritional deficiency:
  - Vitamin B_{12}.
  - Thiamine.
- Cerebellar abscess.

- Drugs (supratherapeutic blood levels):
  - Carbamazepine.
  - Phenytoin.
- Tuberculoma.
- Paraneoplastic syndrome.
- Developmental.
- Arnold–Chiari malformation.
- Dandy–Walker syndrome.
- Paget's disease of the skull.
- Wilson's disease (hepatolenticular degeneration).
- Hypothyroidism.
- Creutzfeldt–Jakob disease (CJD) and other chronic infections.
- Miller Fisher syndrome.
- Normal pressure hydrocephalus.

Ataxia should be distinguished from movement disorders, e.g.

- Chorea: Huntington's, Sydenham's, thyrotoxicosis (very rare).
- Athetosis.
- Hemiballismus: characteristic movement disorder, rare.
- Tardive dyskinesia: chronic phenothiazine therapy.

Investigations

- Cranial CT.
- Magnetic resonance imaging (MRI) brain (if demyelination suspected).
- CXR (cerebellar metastases from bronchogenic carcinoma; paraneoplastic syndrome).
- TFTs.
- Triple evoked potentials (demyelination).
- Lumbar puncture (LP) (➔ Lumbar puncture, pp. 584–9).
- LFTs.
- Serum drug concentrations, especially anticonvulsants.
- Serum vitamin B_{12}.
- Erythrocyte transketolase (↓ in thiamine deficiency, e.g. alcoholism).
- Isotope bone scan (Paget's, metastases).
- Serum alkaline phosphatase (ALP)—bone isoenzyme (Paget's, metastases).
- Urine hydroxyproline (Paget's disease—reflects bone turnover).
- Caeruloplasmin (Wilson's disease).
- Serum and urine copper (Wilson's disease).

Consider whether the movement disorder is psychogenic (uncommon), rather than due to neuropathology. Uncommon and should not be confidently assumed.

➔ *OHCM* 10e, p. 467.

Bradycardia

Bradycardia is defined as a heart rate of <60 beats per minute. It is a normal physiological response to fitness training but should always be considered a marker of potential cardiac disease until proved otherwise.

Causes

A comprehensive history and thorough examination are important. A transient bradycardia can cause disabling symptoms of dizziness or blackouts in the elderly, whilst persistent bradycardia often heralds systemic disease, e.g.:

- *Iatrogenic*: cardiac drugs, e.g. β-blockers (including eye drops for glaucoma), amiodarone, and calcium channel blockers (e.g. diltiazem and verapamil), cause sinus bradycardia; digoxin (atrioventricular (AV) block). The likelihood of extreme bradycardia or heart block is ↑ with combination therapy.
- *Cardiac causes*: acute MI (often transient in inferior MI); coronary artery disease; sick sinus syndrome; myocardial disease (amyloid, Chagas' disease, sarcoid, myocarditis).
- ↑ vagal tone associated with nausea and vomiting.
- Diminished sympathetic activity.
- *Physiological*: bradycardia is normal in sleep and in athletes.
- *Hypothyroidism*: associated with characteristic symptoms and signs.
- ↑ intracranial pressure (ICP), e.g. cerebral tumour.
- *Hypothermia*, e.g. myxoedema coma.
- *Metabolic*: severe hyperkalaemia, anorexia.
- *Toxic:* severe jaundice.
- *Drug toxicity:* opiates.
- *Infective*: inappropriate bradycardia seen in diphtheria, typhoid.

Investigations

- 12-lead ECG to identify the underlying rhythm.

If there are symptoms of chest pain

- Serum troponin and CK.
- Bedside ECG monitoring.
- Exercise ECG.

If there is a history of intermittent dizziness

- 24h ambulatory ECG monitoring, patient-activated event recorder, or implantable loop recorder, depending on the frequency of symptoms.

If indicated by clinical presentation, consider

- TFTs (hypothyroidism).
- Low reading thermometer (hypothermia—check for J waves on ECG).
- CT brain scan (? intracranial pathology).
- U&E.
- LFTs (especially bilirubin).
- Toxicology screen.

➔ *OHCM* 10e, p. 124, p. 808.

Breathlessness

Breathlessness (dyspnoea) is the subjective awareness of difficulty in breathing. Almost universal during exercise, it is a common presenting symptom in a broad spectrum of diseases. A comprehensive history and a thorough examination are therefore essential. Speed of symptom onset, the patient's age and occupation, and local disease prevalence are particularly helpful in devising a differential diagnosis and a guide to investigations.

Causes

- *Acute pulmonary disease*: pneumonia, acute asthma, pulmonary embolus (PE), inhaled foreign body, pneumothorax, acute respiratory distress.
- *Chronic pulmonary disease*: emphysema, chronic bronchitis, ruptured bulla; interstitial disease (sarcoid, fibrosing alveolitis, extrinsic alveolitis, pneumoconiosis).
- *Carcinoma*: bronchogenic carcinoma, lymphangitis carcinomatosis, 2° carcinoma.
- *Acute cardiac disease*: acute MI (and associated complications of pulmonary oedema, ventricular septal defect (VSD), mitral valve chordal rupture and arrhythmias).
- *Chronic cardiac disease*: left ventricular dysfunction, valvular heart disease (mitral or aortic stenosis and regurgitation), ischaemic heart disease (IHD), pulmonary hypertension, pleural effusion, arrhythmias (especially atrial fibrillation (AF)).
- *Metabolic*: poisoning from salicylates, methanol, and ethylene glycol, DKA, lactic acidosis, hepatic and renal failure.
- *Neuromuscular*: intercostal muscle/diaphragmatic weakness due to Guillain–Barré syndrome (GBS), muscular dystrophy.
- *Haematological*: anaemia.
- Anxiety and hyperventilation.
- *Morphological*: kyphoscoliosis, obesity.
- *Laryngeal obstruction*: extrinsic compression (retrosternal goitre), angioedema (often acute drug allergy), laryngeal spasm (hypocalcaemia).

Initial investigations

- FBC.
- U&E.
- Glucose.
- CXR.
- ABGs.
- Peak expiratory flow rate (PEFR).
- 12-lead ECG.

Additional investigations (as indicated)

- Transthoracic echocardiography (TTE).
- 24h ambulatory ECG monitoring.
- Pulmonary function tests.
- CT chest.
- Bronchoscopy.
- Ventilation/perfusion (V/Q) scan/computed tomography pulmonary angiography (CTPA).
- LFTs.
- Ca^{2+}.
- ESR.
- Serum salicylate levels.
- Lactate.
- Lung biopsy.

➔ *OHCM* 10e, p. 782.

Bruising

Easy bruising is a common complaint and warrants careful assessment of onset and nature. Recent onset of spontaneous and unusual bruising or bleeding may suggest a serious acquired defect. A lifelong history of bruising and bleeding (e.g. post-tonsillectomy, dental extraction, or surgery) may imply a congenital defect. Family history may be informative.

Examine: skin, mouth, dependent areas, and fundi for mucocutaneous bleeding and purpura (non-blanching haemorrhages into the skin).

Platelet causes

- Thrombocytopenia or platelet dysfunction (e.g. aspirin).
- Marrow failure, infiltration, immune thrombocytopenia (ITP), DIC, hypersplenism, drugs, or alcohol.

Vascular causes

- Congenital, e.g. Osler–Weber–Rendu syndrome.
- Acquired, e.g. senile purpura, vasculitis (Henoch–Schönlein purpura, infection), diabetes, corticosteroid therapy, scurvy, connective tissue diseases.

Coagulopathy

- Congenital—mucocutaneous bruising is suggestive of a platelet-mediated defect (e.g. von Willebrand's disease, Glanzmann's thrombasthenia), rather than a clotting factor deficiency (e.g. haemophilia A and B).
- Acquired, e.g. DIC, vitamin K deficiency.

Hyperviscosity

- Myeloma, Waldenström's macroglobulinaemia (low-grade lymphoma associated with ↑ IgM and ↑ plasma viscosity), ↑↑ white blood cells (WBC) in leukaemia.

Investigations

- FBC and film.
- Coagulation—international normalized ratio (INR) and activated partial thromboplastin time ratio (APTR).
- Bleeding time, measures platelet and vascular phase.
- DIC screen, including fibrinogen, thrombin time, D-dimers or fibrin degradation products (FDPs).

Consider further tests and referral to haematology for

- Factor assays.
- Platelet aggregation studies to assess platelet function.

➔ *OHCM* 10e, p. 346.

Calf swelling

Assess whether swelling is bilateral or unilateral, precipitating factors, and duration of onset. Careful examination of the affected leg should be extended to a full examination, particularly of the abdominal and cardiovascular systems.

Causes

Venous and lymphatic

- Deep vein thrombosis (DVT).
- Superficial thrombophlebitis.
- Varicose veins.
- Post-phlebitic limb (post-DVT).

Soft tissue/musculoskeletal

- Calf haematoma or trauma.
- Ruptured Baker's cyst (synovial effusion in the popliteal fossa associated with rheumatoid disease).
- Cellulitis (associated fever, sepsis, tachycardia).

Systemic

- CCF (bilateral limb oedema, ↑ JVP, and signs of left ventricular failure (LVF)).
- Hepatic failure.
- Hypoalbuminaemia.
- Nephrotic syndrome.
- Pregnancy: ↑ dependent oedema, but note also ↑ thrombotic risk, and DVT should be excluded.

Deep vein thrombosis (DVT)

Usually affects the lower limb and can extend proximally into the iliofemoral veins and inferior vena cava (IVC), with a higher risk of associated PE and a higher incidence of post-phlebitic limb. Occasionally seen affecting the upper limb, but this is atypical.

Risk factors for DVT

- Age >60 years.
- Previous DVT or PE.
- Recent major surgery, especially orthopaedic lower limb, abdominal, and pelvic.
- Marked immobility.
- Malignancy.
- Pregnancy and postpartum.
- High-dose oestrogen oral contraceptive pill (OCP).
- Family history of venous thromboembolism (VTE).

Investigations

USS Doppler studies, impedance plethysmography, venography, exclude PE. If any associated symptoms, arrange V/Q scan, multislice CT, and pulmonary angiography. Thrombophilia screening for younger patients (age <55), atypical site and extensive clots, spontaneous onset, and family history.

Chest pain

Acute chest pain is a common symptom. A detailed history and a full physical examination should be performed in order to define the most likely cause and necessary investigation pathway.

History

Be sure to ask the following questions about the pain:

- Site and radiation.
- Character.
- Onset and duration.
- Precipitating and relieving features.
- Associated symptoms.
- Response to pain relief, antacids, or nitrates.

Most types of chest pain fall within one of the categories in Table 1.2.

Table 1.2 Pain sources

Pain source	Description of pain
Myocardial ischaemia	Retrosternal, heavy ache, can radiate → jaw and arms, precipitated by exertion, and relieved by rest or nitrates
Aortic dissection	Severe central tearing pain, radiates to back
Gastro-oesophageal disease	Burning central pain; can radiate to shoulders, throat, or abdomen; exacerbated by meals, eased with antacids/milk
Pleuritic pain	Focal sharp pain, exacerbated by inspiration
Pericardial pain	Sharp pain, radiates to left shoulder tip, worse on lying flat and during inspiration, eased by sitting forwards
Musculoskeletal pain	Sharp focal pain exacerbated by movement and palpation

Investigations

(See Table 1.3.)

➔ *OHCM* 10e, p. 36, p. 48, p. 94, p. 784.

Table 1.3 Investigations for suspected diagnoses

Cardiovascular causes: all patients should have a 12-lead ECG and CXR

Suspected diagnosis	Investigations
Myocardial ischaemia/infarction	Serial ECGs
Consider:	Cardiac markers of necrosis
• *Coronary artery disease*	FBC
• *Aortic stenosis*	TFTs
• *Hypertrophic obstructive cardiomyopathy*	Echocardiogram
	Exercise electrocardiogram
	Stress cardiac imaging
	Coronary angiography
Thoracic aortic dissection	FBC, U&E, X-match
Note: myocardial ischaemia may also be present if it involves the coronary arteries	Echocardiogram (TTE or TOE)
	CT, MRI
Syphilitic aortitis	Syphilis serology
Mitral valve prolapse	Echocardiogram (TTE or TOE)
Acute pericarditis	FBC, viral titres, ESR
	Echocardiogram

Pulmonary causes: all patients should have CXR ± ABGs

Suspected diagnosis	Investigations
Pneumonia/pleurisy	FBC, CRP
Acute bronchitis	Sputum and blood cultures
Pulmonary tuberculosis (TB)	Aspiration if empyema suspected
	Early morning urine (TB)
	Mantoux test (TB)
Pneumothorax	CXR
Pulmonary embolus	D-dimers
	12-lead ECG
	V/Q scan
	CT pulmonary angiography
Lung carcinoma	Sputum cytology
Pleural tumour, e.g. mesothelioma	High-resolution CT
Mediastinal tumour	Bronchoscopy
	Tissue biopsy
Gastro-oesophageal causes	
Oesophageal	FBC
• Spasm	G&S
• Oesophagitis	*Helicobacter pylori*
• Candidiasis	Endoscopy
• Reflux disease	Oesophageal manometry
• Mallory–Weiss tear	Oesophageal biopsy

(*Continued*)

Table 1.3 (*Contd.*)

Suspected diagnosis	Investigations
Peptic ulcer disease	Endoscopy Gastrografin® swallow Barium swallow, meal, or follow-through Erect CXR (if perforation suspected clinically)
Acute pancreatitis	Amylase Abdominal USS
Cholecystitis/biliary colic	FBC, CRP, LFTs Urinalysis Abdominal USS ERCP
Musculoskeletal and dermatological causes	
Suspected diagnosis	**Investigations**
Muscular	
Bony structures	
Chest wall bony metastases Rib/sternal fractures Costochondritis (Tietze's syndrome) Ankylosing spondylitis Cervical/thoracic spine disease Thoracic outlet syndrome	CXR Bone scan Spinal X-rays CT scan
Skin/soft tissue	
Acute shingles Post-herpetic neuralgia	Herpetic serology/smear (rarely)

CRP, C-reactive protein; G&S, group and save; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. http://www.onlinejacc.org/content/41/1/159?_ga=2.15239422.956431479.1499776108-163922176.1499776108.

Clubbing

Soft tissue hypertrophy under the nail bed distorts finger and toenail growth.

Characteristic features

- ↑ lateral and longitudinal nail curvature.
- The skin at the base of the nail becomes spongy.
- The angle between the nail and skin is obliterated.
- In extreme cases, the terminal phalanx becomes bulbous like a drumstick.

Clubbing can be an important visual indicator of major disease, although it can also be congenital. Rarely, clubbing may accompany swollen wrists and ankles as part of a proliferative periostitis seen in hypertrophic pulmonary osteoarthropathy (HPOA). This is associated with squamous carcinoma of the lung.

Major causes

- *Lung disease*: cystic fibrosis, bronchiectasis, empyema, lung abscess, asbestosis, mesothelioma, pulmonary sarcoid.
- *Carcinoma*: bronchogenic (especially squamous cell), mediastinal, pleural, oesophageal, gastric, colonic, thoracic lymphoma, familial polyposis coli.
- *Infection*: infective endocarditis, colonic amoebiasis.
- *Vascular disease*: cyanotic congenital heart disease, atrial myxoma, arteriovenous malformation (AVM).
- *Liver disease*: primary biliary cirrhosis (PBC), chronic active hepatitis.
- Ulcerative colitis and Crohn's disease, malabsorption.
- *Rare causes*: thyrotoxicosis, polycythaemia, SLE.

Investigations

As guided by differential diagnosis and clinical suspicion

- FBC.
- ESR.
- C-reactive protein (CRP).
- LFTs.
- TFTs.
- Serum ACE.
- Autoantibodies.
- Blood cultures (at least three sets if infective endocarditis suspected).
- Faecal occult blood (FOB) (three samples).
- CXR.
- Echocardiography (TTE or transoesophageal echocardiography (TOE)).
- OGD and biopsy.
- Colonoscopy and biopsy.
- Abdominal USS.
- CT chest.
- Bronchoscopy, biopsy, washings.
- Liver biopsy.

➔ *OHCM* 10e, p. 40, p. 77.

Coma

The Glasgow Coma Scale (GCS) is used to assess the level of consciousness (see Table 1.4). The minimum score is 3; the maximum 15.

Assess the level of consciousness and determine whether this is stable, fluctuating, improving, or deteriorating on serial assessments.

Cerebral causes

- Intracranial haemorrhage (subarachnoid haemorrhage (SAH), subdural haemorrhage (SDH), extradural haemorrhage (EDH), intracerebral bleed).
- Large cerebral infarct.
- Pontine haemorrhage (pinpoint pupils).
- Cerebral venous sinus thrombosis.
- Hypertensive encephalopathy.
- Cerebral tumour (associated local cerebral oedema may respond to dexamethasone).
- Head injury.
- Cerebral infection—encephalitis, meningitis, cerebral malaria, brain abscess.
- Post-ictal state.
- Subclinical status epilepticus. (*Note*: this is an EEG diagnosis.)
- Cerebral vasculitis, e.g. SLE.
- End-stage MS.
- Leukodystrophy.
- CJD (including variant CJD (vCJD)).

Table 1.4 Glasgow Coma Scale

Eye opening	1	Nil
	2	To pain
	3	To voice
	4	Spontaneously
Motor response	1	Nil
	2	Extension
	3	Flexion
	4	Withdrawal from pain
	5	Localizing to pain
	6	Voluntary
Vocal response	1	Nil
	2	Groans
	3	Inappropriate words
	4	Disorientated speech
	5	Orientated speech

Metabolic causes

- Drugs (usually in deliberate overdose; ➔ Chapter 11).
- Alcohol excess. (*Note*: remember hypoglycaemia as a cause of coma in alcoholics, as well as extradural haematoma.)
- Hypoglycaemia (iatrogenic, overdose of insulin or sulfonylureas, insulinoma, insulin-like growth factor (IGF)-2-associated hypoglycaemia in certain tumours).
- DKA (coma in ~10% of cases—adverse prognostic sign).
- Hyperosmolar non-ketotic coma (HONK) (may present as severe dehydration ± coma).
- Uraemia.
- Late stages of hepatic encephalopathy.
- Severe hyponatraemia (relatively common—especially inappropriate antidiuretic hormone (ADH) syndrome).
- Hypothyroidism (myxoedema coma—rare).
- Hypercalcaemia.
- Inborn error of metabolism, e.g. porphyria, urea cycle disorders.
- Type 2 respiratory failure (carbon dioxide (CO_2) narcosis).
- Hypothermia (severe).
- Hyperpyrexia (neuroleptic malignant syndrome (NMS), after anaesthesia).
- Severe nutritional deficiency—thiamine, pyridoxine, vitamin B_{12}.

Investigations

- Venous plasma glucose (exclude hypoglycaemia with a fingerstick + reflectance meter; confirm with a venous plasma fluoride–oxalate sample).
- U&E.
- LFTs.
- Serum Ca^{2+}.
- Serum osmolality.
- Urine Na^+.
- Blood cultures.
- Clotting screen (➔ p. 288, p. 289, p. 290).
- ABGs.
- Drug screen (serum, urine).
- Cranial CT scan.
- LP.
- CXR (bronchogenic carcinoma with cerebral metastases).
- 12-lead ECG.
- EEG.
- Erythrocyte transketolase (↓ in thiamine deficiency).
- Serum ammonia (NH_3) (↑ in urea cycle disorders).
- Brain biopsy.

Always assess Airway, Breathing, Circulation before assessment of the cause of ↓ consciousness. Consider psychogenic unresponsiveness.

➔ *OHCM* 10e, p. 220, pp. 786–9, p. 834, p. 836.

Confusion

A reliable witness, family member, or carer may be vital in assessing a patient with confusion, and care must be taken to discriminate between acute and chronic symptoms. Acute confusional states carry a very broad differential diagnosis and require careful initial evaluation (see Table 1.5). Any systemic illness can precipitate a confusional state.

Investigations

- FBC, U&E, LFTs, serum Ca^{2+}, BM stix, and blood glucose.
- ABGs.
- MSU, blood cultures, sputum culture.
- CXR.
- ECG.
- Thyroid function.
- Drug/toxicology screen—blood and urine.
- CT scan.
- LP.

►► Always look for a MedicAlert™ bracelet, necklace, or card.

Table 1.5 Causes of confusion

Hypoxaemia	Acute infection, asthma, COPD, etc.
Head injury	Cerebral trauma
Vascular	CVA, TIA, intracerebral, SDH
Infection	Systemic Meningitis or encephalitis
Endocrine/metabolic	DKA, hypoglycaemia, thyrotoxicosis or myxoedema, uraemia, hypercalcaemia, hyponatraemia
Alcohol and drug abuse	Acute intoxification and withdrawal Also consider overdose
Iatrogenic	Full and recent medication history (especially opiates, analgesia, and sedatives)
Post-ictal state	
Cerebral tumour	
Psychiatric	
Wernicke's encephalopathy	

OHCM 10e, p. 576.

Constipation

Patients may use the term constipation to mean infrequent, hard, small volume, or difficult to pass faeces. Patients vary enormously in their threshold to seek medical advice about bowel habit.

Ask about:

- Associated pain.
- PR bleeding.
- Tenesmus.
- Weight loss.

Causes

- Carcinoma of the colon.
- Diverticular disease.
- Anorectal disease—fissure or haemorrhoid.
- Benign stricture.
- Rectocele.
- Sigmoid volvulus.
- Hernia.
- Drugs, especially analgesics.
- Poor fluid intake.
- Low-fibre diet.
- Change in diet.
- Immobility.
- IBS.
- Megarectum.
- Hirschsprung's disease.
- Spinal cord lesion.
- Stroke.
- Jejunal diverticulosis.
- Hypothyroidism.
- Diabetic neuropathy.
- Hypercalcaemia, hyperparathyroidism, hypokalaemia.
- Uraemia.
- Porphyria.
- Pregnancy.
- MS.
- PD.
- Dermatomyositis.
- Myotonic dystrophy.
- Scleroderma.
- Psychological.

Investigations

- Digital rectal examination.
- Proctoscopy.
- Sigmoidoscopy.
- Colonoscopy.
- Barium enema.
- U&E.
- Ca^{2+}.
- TFTs.
- FBC.
- Bowel transit time studies.
- Anorectal manometry.
- Electrophysiological studies.
- Defecating proctography.

►► Elderly patients are more prone to constipation.

➔ *OHCM* 10e, pp. 260–1, p. 534.

Cyanosis

Cyanosis is a blue/purple dusky discoloration of tissue caused by a rise in blood deoxygenated Hb content (>5g/dL). Rarely it may be caused by ↑ sulphaemoglobin, methaemoglobin, or COHb. Cyanosis may be peripheral affecting only cutaneous areas, or central when mucous membranes of the mouth and tongue are also discoloured.

Causes of peripheral cyanosis

- Central cyanosis.
- Shock.
- Hypothermia.
- Mitral stenosis.
- Raynaud's syndrome.
- Peripheral arterial disease.
- Patent ductus arteriosus (differential cyanosis, i.e. cyanosed toes, but not fingers, is pathognomonic of this condition).

Causes of central cyanosis

Pulmonary disease with severely impaired oxygen transfer

- Pneumonia.
- Asthma.
- Chronic obstructive pulmonary disease (COPD).
- PE.
- Fibrosing alveolitis.

Right-to-left shunt (Eisenmenger's syndrome)

- Atrial septal defect.
- VSD.
- Patent ductus arteriosus.
- Partial anomalous pulmonary venous drainage (APVD).
- AVM.

Methaemoglobinaemia, sulphaemoglobinaemia, carboxyhaemoglobinaemia

- Congenital.
- Ingestion of oxidizing agents, e.g. phenacetin, inorganic nitrates, local anaesthetic.

Cyanosis arising from pulmonary disease can be reversed by administration of oxygen (O_2) to improve alveolar O_2 uptake. O_2 has no effect where right-to-left shunts are the cause. Central cyanosis may be underestimated with significant anaemia and is more apparent in patients with polycythaemia. In methaemoglobinaemia, the arterial concentration of O_2 is normal. This condition can be treated with IV methylthioninium chloride (methylene blue) (➔ Chapter 11).

Investigations

- FBC.
- ABGs.
- CXR.
- 12-lead ECG.
- TTE (proceeding to TOE if shunt is suspected).
- CT chest (if AVM is suspected).
- Cardiac MRI (if APVD is suspected).

➔ *OHCM* 10e, p. 34.

Diarrhoea

Patients may use the term diarrhoea to describe loose stools, ↑ frequency of defecation, ↑ volume of stool, steatorrhoea, melaena, or faecal incontinence (➔ Incontinence: faecal, p. 60).

Ask about

- Duration.
- Associated features (abdominal pain, vomiting, mucus, or blood PR).
- Systemic symptoms.
- Recent foreign travel.
- Suspect food.
- Is anyone else in the household affected?

Causes

- Infection (including 'traveller's diarrhoea').
- IBD.
- Diverticular disease.
- Colonic carcinoma.
- Other tumour, especially villous adenoma.
- Coeliac disease.
- Tropical sprue.
- IBS.
- Ischaemic colitis/bowel infarction.
- Laxative use!
- Other drugs, e.g. metformin, orlistat.
- Overindulgence in fruit or vegetables.
- Overflow 2° to constipation.
- Carcinoid syndrome (uncommon).
- Gastrinoma (rare).
- VIPoma (rare).
- Glucagonoma (very rare).
- Hyperthyroidism (common).
- Medullary carcinoma of the thyroid (uncommon).
- Bile salt diarrhoea (previous ileal disease or surgery).
- Dumping syndrome (previous gastric surgery).
- Gut motility disorders.
- Malabsorption (cf. pancreatitis, lymphangiectasia, coeliac).
- Lactose intolerance.
- Scleroderma.
- Amyloidosis.
- Whipple's disease.

Investigations

- Stool culture, hot stool for parasites.
- *Clostridium difficile* toxin in stool.
- High rectal swab for parasites. (*Note*: giardiasis is diagnosed on duodenal biopsy.)
- Rectal examination, proctoscopy, sigmoidoscopy ± biopsy.
- Colonoscopy.

- AXR.
- Barium enema.
- Small bowel follow-through contrast studies.
- Upper GI endoscopy.
- Small bowel biopsy.
- FBC and blood film.
- ESR.
- CRP.
- Serum ferritin and folate.
- U&E (exclude haemolytic uraemic syndrome (HUS), especially in children).
- Urine screen for laxatives.
- Antigliadin, antiendomysial antibodies and anti-tissue transglutaminase (tTG) (coeliac disease).
- TFTs.
- Serum gut hormone profile (gastrin, vasoactive intestinal peptide (VIP), glucagon—seek expert advice).
- 24h urine for 5-hydroxyindole acetic acid (5HIAA).
- Serum calcitonin (medullary carcinoma of the thyroid).
- Lactose hydrogen breath test (for lactose intolerance).
- ^{14}C-xylose breath test (bacterial overgrowth in the small bowel).
- CT abdomen.
- Mesenteric angiography (ischaemia).

Investigations must be guided by history and examination findings. If the patient is an inpatient, they should be isolated until infection is excluded. Consider HIV and other immune disorders if an unusual bowel organism is found.

Dizziness and syncope

Dizziness is a term that may be used to describe a variety of symptoms, e.g. spinning (rotatory vertigo), light-headedness, muzzy feeling, or unsteadiness on walking. It is therefore important to establish precisely what the patient means by dizziness.

Loss of consciousness or 'blackout' may not be reported by the patient and an eyewitness account is important. Enquire about any awareness of abnormal heart beat (rhythm-induced syncope), chest pain (ischaemia), neurological symptoms (cerebrovascular disease), preceding micturition, change of posture, or unusual sensations (prodromal epileptic symptoms, e.g. strange taste or smell) prior to the collapse.

Causes of dizziness

- Rotatory sensation lasting >10s and precipitated by movement or position—vestibular cause such as labyrinthitis, Ménière's disease, cerebello-pontine angle tumour (acoustic neuroma).
- Rotatory sensation lasting 2 or 3s and precipitated by movement—cervical spondylosis.
- Non-rotatory sensation lasting 2 or 3s and precipitated by movement, position, or standing up—cervical spondylosis, cerebrovascular disease, postural hypotension, cardiac arrhythmia (usually back to normal in minutes), epilepsy (incontinence is common and return to normal may take hours).

Investigations

Suspected vestibular cause

- Hallpike manoeuvre.
- MRI or CT cerebello-pontine angle.
- Audiometry.

Suspected non-vestibular cause

- Blood glucose.
- 12-lead ECG.
- 24h ambulatory ECG monitoring.
- EEG.
- MRI or CT head.
- Tilt table test.

Causes of syncope

- Vasovagal: pain, fear, prolonged standing, excess heat, alcohol, or food.
- Micturition (often elderly men standing up during the night to urinate).
- Defecation (often elderly women with constipation).
- Coughing: chronic airways disease.
- Orthostatic hypotension:
  - Autonomic dysfunction (diabetic neuropathy, Shy–Drager syndrome).
  - Drugs (antihypertensives, diuretics, nitrates, tricyclics; dehydration and sodium depletion).
- Carotid sinus syndrome.
- Epilepsy.

- Drugs: alcohol, illicit drugs.
- Cardiac: arrhythmias, outflow obstruction (aortic stenosis, hypertrophic obstructive cardiomyopathy, myxoma).
- Hyperventilation and anxiety.
- Acute cerebrovascular disease: transient ischaemic attack (TIA), stroke, SAH.
- Acute vascular obstruction: PE, MI.
- Hypoglycaemia: poorly controlled diabetes.

Investigations

- 12-lead ECG.
- 24h Holter monitoring.
- Echocardiography.
- MRI or CT head.
- Tilt table test.
- Blood glucose, HbA_{1c}.
- U&E.
- Cardiac markers.
- ABG.
- Toxicology screen.
- V/Q scan.

► Driving and dizziness/syncope

For guidance on driving in the United Kingdom (UK), see http://www.dvla.gov.uk.

Further reading

Brignole M, Alboni P, Benditt DG, *et al.*; Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2004; **25**: 2054–72.

Dysarthria and dysphasia

Dysarthria is difficulty in articulating words. The patient may complain of 'slurred speech'. Dysphasia is a difficulty in the formation of speech due to interference with higher mental function. These disturbances often occur together, most commonly in the context of a stroke.

Damage to Wernicke's area causes a *receptive* dysphasia. Speech may be fluent, but meaning is lost. Damage to Broca's area causes an *expressive* dysphasia. Speech is non-fluent and the patients are aware they are not using the right words.

Causes of dysphasia include stroke (usually with right hemiparesis, arm more affected than leg) or SOL. Psychosis, especially schizophrenia, may cause a similar picture—the so-called 'word salad'.

Causes of dysarthria

- Stroke (internal capsule or extensive lesion of the motor cortex—acute).
- Motor neurone disease (MND).
- Midbrain or brainstem tumour.
- PD.
- Cerebellar disease (haemorrhage, infarct, MS, hereditary ataxia, alcoholic or paraneoplastic degeneration).
- Syringobulbia (chronic, progressive).
- Neuromuscular (myasthenia gravis (MG), dermatomyositis, myotonic dystrophy).
- Acute alcohol or drug intoxication.

Dysarthria may be more obvious when the (English-speaking!) patient is invited to say '*Baby hippopotamus*', '*British constitution*', etc.

Investigations

- Cranial CT scan.
- Venous plasma glucose.
- ESR.
- Serum lipids.
- 12-lead ECG.
- Echocardiogram.
- Carotid Doppler studies (especially if bruit).
- CXR.
- LFTs.

Less commonly

- Serum muscle enzymes (polymyositis).
- Autoimmune profile.
- Electromyogram (EMG).
- Skeletal muscle biopsy.

➔ *OHCM* 10e, pp. 86–7.

Dysphagia

Dysphagia is difficulty in swallowing. The patient may have associated odynophagia (painful swallowing) or regurgitation of food (immediate or delayed?). Elicit whether the dysphagia is for liquid, solids, or both. Is it intermittent or progressive? Are there associated symptoms?

A careful physical examination is mandatory. Pay special attention to the lower cranial nerves; search for lymph nodes in the supraclavicular fossae. Palpate the thyroid and percuss for retrosternal enlargement.

Causes

- Oesophageal carcinoma.
- Benign oesophageal stricture 2° to chronic acid reflux.
- Barrett's oesophagus.
- Achalasia or diffuse spasm.
- Stroke (bilateral internal capsule cerebrovascular accidents (CVAs)—pseudo-bulbar palsy).
- Oesophageal web (+ iron deficiency anaemia = Plummer–Vinson (Patterson–Kelly–Brown) syndrome).
- Pharyngeal pouch.
- Muscular problem (MG, dermatomyositis, myotonic dystrophy).
- Bulbar palsy (MS, MND, poliomyelitis).
- Scleroderma (including CREST syndrome—➔ *OHCM* 10e, Chapter 12).
- Infection (usually acute pain on swallowing).
- Mediastinal mass (goitre, carcinoma of the bronchus, enlarged left atrium, aortic aneurysm).

Investigations

- FBC.
- ESR.
- Upper GI endoscopy.
- Barium swallow.
- CXR.
- Oesophageal manometry studies (➔ Gastrointestinal physiology, pp. 526–7).
- Cranial CT or MRI (if neurological signs).
- Acetylcholine (ACh) receptor antibodies and Tensilon® (edrophonium). test if MG is suspected (➔ Edrophonium (Tensilon®) test, p. 631).

Note: consider HIV testing if there is oesophageal *Candida*, or herpes simplex or cytomegalovirus (CMV) infection in the oesophagus.

➔ *OHCM* 10e, p. 64, pp. 250–1.

Facial pain

Is the pain unilateral or bilateral? Is it constant or intermittent? Precipitating factors or trigger points? A full examination of the head and neck is required in addition to a detailed neurological and systemic examination.

Causes

- Trigeminal neuralgia (TN).
- Temporal arteritis (TA). ►► Risk of visual loss (➔ *OHCM* 10e, Chapter 11).
- Herpes zoster (shingles or post-herpetic neuralgia).
- Dental caries, sepsis.
- Sinusitis.
- Temporomandibular joint dysfunction.
- Cluster headache.
- Glaucoma.
- Angina pectoris.
- Tonsillitis.
- Syringobulbia.
- Atypical facial neuralgia.
- Migraine.

Investigations

- ESR—urgent in suspected TA.
- Temporal artery biopsy if TA strongly suspected. (►► Must be performed rapidly—*within days*—if steroid treatment is commenced. However, do not withhold corticosteroid therapy for this reason!) Because of 'skip' lesions, false −ve biopsies may be encountered. Be guided by the full clinical picture, rather than reliance on a single test.
- Plain radiographs or CT imaging of frontal or maxillary sinuses.
- MRI to exclude MS, basilar aneurysm, trigeminal schwannoma, neurofibroma as causes of TN.
- MRI of the cervical spinal cord to exclude syringobulbia if pain is accompanied by brainstem signs.

➔ Headache, pp. 49–50 and ➔ *OHCM* 10e, p. 64, pp. 456–7.

Fever of unknown origin (FUO or PUO)

Defined as temperature >38.3°C on several occasions, lasting 3 weeks or more. It is very important to take a full history and consider infectious contacts, recent travel abroad, recent surgery and dental treatment, sexual history, and risk factors for HIV.

Signs

Examine for heart murmurs, splinter haemorrhages, splenomegaly, lymphadenopathy, and rashes/pruritus (see Table 1.6).

Table 1.6 Causes of FUO/PUO

Infection	Abscesses (e.g. subphrenic, pelvic, lung), osteomyelitis, TB, endocarditis, parasites, rheumatic fever, brucellosis, toxoplasmosis, Lyme disease, histoplasmosis, viral (especially Epstein–Barr virus, CMV, hepatitis, and HIV)
Malignancy	Lymphoma, leukaemia, hypernephroma, ovary, lung, hepatoma
Connective tissue	Polyarteritis nodosa, SLE, RhA, Still's disease, TA
Other	Sarcoidosis, atrial myxoma, drug fever, IBD, factitious

Investigations

- Re-take the history and re-examine the patient (something might have been missed or new symptoms/signs may have developed).
- FBC, ESR.
- U&E, LFTs, Ca^{2+}.
- CXR.
- MSU, urinalysis.
- Serology for *Brucella* and *Toxoplasma*.
- All biopsy material should be sent for culture, including TB.
- Blood cultures (serial may be necessary).
- Monospot/Paul Bunnell.
- Autoimmune profile (antinuclear antibodies (ANA), rheumatoid factor (RF), ANCA, etc.).
- Bone marrow aspirate/trephine/culture for TB with Ziehl–Neelsen (ZN) stain.
- Abdominal USS (? masses).

Extend investigations as below according to symptoms and signs

- Consult microbiology or infectious disease consultant for advice.
- Stool cultures and fresh stool for ova, cysts, and parasites.
- Repeat serological investigation for changing titres (2–3 weeks).
- Thick and thin blood film for malaria and parasites.
- Mantoux.
- TTE or TOE to exclude endocarditic vegetations.
- CT chest, abdomen, and pelvis.

►► Always re-examine the patient for evolving new signs if the cause remains unknown.

➲ *OHCM* 10e, pp. 442–3.

First fit

►► A first fit in an adult requires careful evaluation since the probability of an underlying structural lesion ↑ with age.

Take a careful history, preferably from a witness as well as the patient. Most lay persons will recognize a generalized tonic–clonic fit. However, the occurrence of a few 'epileptiform' movements in patients with syncopal episodes (➔ Dizziness and syncope, pp. 34–5) may cause diagnostic uncertainty.

Be sure to ask about

- Aura preceding the episode. ► Temporal lobe epilepsy—olfactory or gustatory auras (not necessarily followed by convulsions).
- Loss of consciousness—how long? Often overestimated by witnesses!
- Tongue biting.
- Focal or generalized convulsive movements. *Note*: a clear history of a tonic–clonic fit commencing in a limb and progressing to a more generalized convulsion is highly suggestive of a structural intracerebral lesion; cranial imaging is mandatory.
- Central cyanosis (tonic phase).
- Urinary incontinence.
- Injuries.
- Post-ictal confusion.
- History of trauma.
- Alcohol intake. *Remember*: alcohol withdrawal fits as well as acute intoxication.
- Drug history—prescribed and recreational.
- History of insulin-treated diabetes or type 2 diabetes treated with oral secretagogues, i.e. sulfonylureas, repaglinide, nateglinide. *Note*: metformin and thiazolidinediones as monotherapy do not cause significant hypoglycaemia.

A full general and neurological examination is needed, specifically including:

- Fever.
- Meningism, i.e. nuchal rigidity, +ve Kernig's sign (meningoencephalitis).
- Cutaneous rash or ecchymoses (? bleeding diathesis).
- Evidence of head trauma (preceding fit or as a consequence).
- Signs of chronic liver disease.
- Focal neurological deficit. ► Third nerve palsy in an intracranial SOL, including aneurysm of the posterior communicating artery. Sixth nerve lesion may act as a 'false localizing sign' in ↑ ICP.
- MedicAlert™ bracelet (history of epilepsy or diabetes—search personal belongings).

Bilateral extensor plantar reflexes can occur after a generalized fit without a structural brain lesion and there may be transient hemiparesis (Todd's paresis).

Causes

- Epilepsy (➔ *OHCM* 10e, Chapter 10).
- Hypoglycaemia (acute, severe, history of diabetes?).
- Hyponatraemia (usually <110mmol/L or rapid development).
- Hypocalcaemia (➔ *OHCM* 10e, Chapter 14).
- Hypomagnesaemia (may accompany hypocalcaemia).
- Hypophosphataemia (rare).
- Alcohol withdrawal. ▶▶ Risk of associated hypoglycaemia.
- Discontinuation of anticonvulsant medication.
- Infection—viral encephalitis or bacterial meningitis. ▶▶ Consider intracerebral abscess, tuberculoma in predisposed patients.
- Encephalopathy—hepatic, uraemic, hypertensive, thyrotoxic (rare—'thyroid storm').
- Eclampsia.
- Porphyria.
- Cerebral SLE.
- Head injury.
- Hypoxia.
- Cerebral tumour.
- Stroke—cerebral infarct, haemorrhage.

Investigations

- Venous plasma glucose (fingerprick test at bedside useful as 'screen'—but can be unreliable).
- U&E.
- Serum Ca^{2+}, magnesium (Mg^{2+}), phosphate (PO_4^{3-}).
- Cranial CT or MRI scan.
- EEG.
- LP (➔ Lumbar puncture, pp. 584–9).
- CXR.
- Serum prolactin (PRL) (may be ↑ after generalized convulsions, but not pseudo-seizures).
- ABGs—remember transient lactic acidosis following generalized tonic–clonic convulsions.
- Blood ethanol (may be undetectable in withdrawal state).
- Serum or urine drug screen.

'Pseudo-seizures' may be encountered in patients with atypical recurrent fits (usually long history of epilepsy) and this is unlikely in an adult presenting with a first fit. ▶ In UK, the DVLA prohibits driving for 12 months following a first fit.

➔ *OHCM* 10e, pp. 490–2.

Galactorrhoea

Denotes inappropriate breast milk production, i.e. in the absence of pregnancy. The commonest cause is hyperprolactinaemia (↑ PRL) due to a pituitary microprolactinoma of <10mm in diameter (➔ Precocious puberty, p. 179). Prolactinomas (usually macroadenomas) may cause galactorrhoea in men.

Note: other disease in the pituitary region, certain drugs, and several systemic disorders may be associated with ↑ PRL (➔ *OHCM* 10e, Chapter 5).

Causes

Normoprolactinaemic galactorrhoea

- This has been described in premenopausal women occurring after the conclusion of:
  - Treatment with the combined contraceptive pill.
  - Breastfeeding (for >6 months afterwards).
- ↑ sensitivity of lactogenic tissue PRL is postulated, but the mechanism remains uncertain. In part, this may reflect difficulties that can arise in determining whether PRL is persistently elevated. Menstrual disturbances have been described.

Hyperprolactinaemia

- The differential diagnosis and investigation of hyperprolactinaemia are considered in ➔ Galactorrhoea (hyperprolactinaemia), pp. 172–3.

Investigations

- Serum PRL (➔ Galactorrhoea (hyperprolactinaemia), pp. 172–3).
- Repeated measurements under controlled conditions may be required since PRL is a 'stress' hormone and may be ↑ by venepuncture.

Note: if ↑ PRL is confirmed, further investigations to exclude causes other than a prolactinoma are required.

- Pituitary imaging (CT, or preferably MRI) and visual field testing (Goldmann) may also be indicated if a macroprolactinoma is suspected (PRL concentrations usually very high).

Note: if there is doubt about the nature of the nipple discharge, further specialized investigations may be required on the fluid, including:

- Casein.
- Lactose.
- Microscopy.

Clear fluid may result from benign breast disease.

Note: bloody discharge should prompt urgent specialist investigations to exclude carcinoma of the breast:

- Mammography.
- Biopsy.

➔ *OHCM* 10e, p. 237.

Further reading

Kleinberg DL, Noel GL, Frantz AG. Galactorrhoea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977; **296**: 589–600.

Gout

Gout is a disease of deposition of monosodium urate monohydrate crystals in tissues and relates to hyperuricaemia. Hyperuricaemia is due to an imbalance between purine synthesis and uric acid excretion. Episodes of acute gout may be precipitated by alcohol, trauma, dietary changes, infection, chemotherapy, or surgery. Commoner in men and very rare in premenopausal women.

Clinical features

- Inflammatory arthritis, classically monoarthritis or oligoarthritis affecting the first metatarsophalangeal (MTP) joint of the foot but can affect any joint, including the spine.
- Tenosynovitis.
- Bursitis or cellulitis.
- Tophi—urate deposits in tendons, ear pinnae, and joints.
- Urolithiasis and renal disease.

Investigations

- ESR (may be ↑).
- Urate crystals demonstrated in the synovial fluid or tissues—negatively birefringent on polarized light microscopy.
- Serum urate (not always ↑ in an acute episode, and a normal urate level does not exclude the diagnosis).
- X-ray—soft tissue swelling and punched-out bony erosions.
- Autoimmune profile (AIP) (to exclude rheumatoid).
- Microscopy of synovial fluid (Gram stain and culture).

Treatment

Acute episode

- NSAIDs, colchicine, intra-articular steroids, or oral steroids.
- Avoid precipitating factors and purine-rich foods.
- Urate-lowering therapy indicated for tophi, recurrent attacks, and urine/renal disease, e.g.
  - Allopurinol (xanthine oxidase inhibitor).
  - Probenecid (uricosuric).

Note: asymptomatic hyperuricaemia is commoner than gout, and a high serum urate level with coexistent arthritis is not necessarily due to crystal deposition. Consider important other causes, especially infective arthritis and pseudo-gout.

Pseudo-gout

Calcium pyrophosphate crystal deposition causing acute arthritis or chondrocalcinosis. Crystals are weakly positively birefringent on polarized light microscopy. Associations include old age, dehydration, hyperparathyroidism, hypothyroidism, haemochromatosis, acromegaly, RhA, and osteoarthritis (OA).

➔ *OHCM* 10e, p. 548.

Gynaecomastia

Gynaecomastia is benign bilateral hyperplasia of glandular and fatty breast tissue in the ♂. The balance between androgens and oestrogens is thought to be of importance in the pathogenesis; many conditions may influence this ratio. Most commonly, it appears transiently during normal puberty (detectable at some stage in ~50% of cases). Gynaecomastia may also be caused by specific endocrine disease or be associated with certain chronic diseases. Treatment with certain drugs is a common cause (~30% of cases) and arises via several mechanisms. Investigations will be guided by the individual circumstances. A careful drug history and thorough physical examination are required, particularly in the post-adolescent period.

When indicated, and after excluding causes such as congenital syndrome and drug therapy, investigations are principally directed at:

- Excluding endocrine carcinoma (rare).
- Identifying associated chronic diseases.

Note:

- Simple obesity is not usually a cause of true gynaecomastia, i.e. the glandular element is not ↑.
- ↑ serum PRL in isolation does not cause gynaecomastia.
- Unilateral, eccentric breast enlargement should prompt exclusion of breast carcinoma (rare).

Causes include

- Physiological states (transient):
  - Newborn.
  - Puberty.
  - Advanced age.
- Klinefelter's syndrome (47,XXY; mosaics).
- 2° hypogonadism, e.g. mumps orchitis.
- Androgen resistance syndromes, e.g. testicular feminization.
- ↑ tissue aromatase activity (converts androgens to oestrogens).
- Oestrogen-producing tumours:
  - Leydig cell tumour.
  - Sertoli cell tumour.
  - Adrenal carcinoma.
- Chronic liver disease.
- Chronic renal failure.
- Panhypopituitarism.
- Tumours producing human chorionic gonadotrophin (hCG).
- Drugs: oestrogens (prostatic carcinoma, transsexuals), spironolactone, cimetidine, digoxin, cytotoxic agents, marijuana.
- Hyperthyroidism (↑ serum sex hormone-binding globulin (SHBG)).
- 1° hypothyroidism.
- Cushing's syndrome.
- Carcinoma of the bronchus.
- Idiopathic.

Investigations

- Testosterone.
- FSH.
- LH.
- LFTs.
- TFTs.
- Oestradiol.
- β-hCG.
- PRL.
- SHBG (affinity of SHBG is higher for testosterone than for oestrogens, therefore ↑ SHBG causes disproportionate ↓ in free testosterone levels).
- Dehydroepiandrosterone sulfate (DHEAS).
- Androstenedione.
- Testicular USS.
- CXR.
- Abdominal CT or MRI imaging (for suspected adrenal tumours).
- Pituitary imaging.
- Karyotype.
- Urinary 17-oxo-steroids.

If carcinoma of the breast is suspected

- Mammogram.
- Fine-needle aspiration (FNA).

➔ *OHCM* 10e, p. 230.

Further reading

Braunstein GD. Gynecomastia. *N Engl J Med* 1994; **328**: 490–5.

Haematemesis

This literally means vomiting blood and is often associated with melaena (passage of black tarry stools).

Causes

- Chronic peptic ulceration (e.g. duodenal ulcer (DU) or gastric ulcer (GU)) accounts for 50% of cases of bleeding from the upper GI tract.
- Acute GUs or gastric erosions.
- Drugs (e.g. NSAIDs) or alcohol.
- Reflux oesophagitis.
- Mallory–Weiss tear.
- Oesophageal varices.
- Gastric carcinoma (uncommon).

Investigations after admission and stabilization of the patient

- Full history, including drugs, alcohol, past history, indigestion, etc.
- FBC. (*Note*: Hb will take ~24h to fall; initially may be normal.)
- U&E.
- Cross-match blood.
- Urgent upper GI tract endoscopy.
- Check *Helicobacter pylori* serology ± urea breath test.

➔ *OHCM* 10e, p. 30, p. 256.

Haematuria

In health, adults pass between 500,000 and 2,000,000 red cells over a 24h period. Haematuria implies the passage of excess blood that may be detectable using dipsticks (microscopic haematuria) or may be obvious to the naked eye (macroscopic haematuria).

Causes

- Many.
- Glomerular disease, e.g. 1° glomerulonephritis, 2° glomerulonephritis (SLE, vasculitis, infection).
- Vascular or interstitial disease due to hypersensitivity reactions, renal infarction, papillary necrosis, or pyelonephritis.
- Trauma.
- Renal epithelial or vascular tumours.
- Lower renal tract disease, e.g. tumours, stones, infection, drug toxicity (e.g. cyclophosphamide), foreign bodies, or parasites.
- Systemic coagulation abnormalities, e.g. platelet or coagulation factor abnormalities such as profound thrombocytopenia or DIC.

Investigations

- Urinalysis—dipstick, microscopic examination, culture.
- Radiology,* e.g. KUB or IVU.
- Specialist investigation,* e.g. angiography, CT or MRI scanning.
- Cystoscopy.*

Note: ideally these tests (*) should be arranged after discussion with either a nephrologist or a urologist.

➔ *OHCM* 10e, p. 80, p. 294.

Haemoptysis

This describes coughing up blood or bloodstained sputum and can vary from faint traces of blood to frank bleeding. Before embarking on investigation, it is essential to ensure that the blood is coughed up from the respiratory tract and is not that of epistaxis or haematemesis (easily confused).

Causes

- Infective, e.g. acute respiratory infection, exacerbation of COPD.
- Pulmonary infarction, e.g. PE.
- Lung cancer.
- TB.
- Pulmonary oedema.
- Bronchiectasis.
- Uncommon causes, e.g. idiopathic pulmonary haemosiderosis, Goodpasture's syndrome, microscopic vasculitis, trauma, haematological disease (e.g. ITP or DIC).

Investigations

- Colour of blood provides clues (pink frothy in pulmonary oedema, rust-coloured in pneumonia).
- Check oxygen (O_2) saturation.
- FBC (? ↓ platelets).
- ESR.
- Coagulation screen.
- Sputum culture.
- CXR.
- Arrange bronchoscopy after discussion with the respiratory team.

➔ *OHCM* 10e, pp. 48–9.

Headache

➔ Facial pain, p. 38.

Headache is an extremely common complaint. Most patients self-medicate and only a small proportion will seek medical advice. Headache may be acute or chronic, constant, recurrent, or gradually progressive. It may arise from structures within the cranial vault or from external causes (➔ *OHCM* 10e, Chapter 10).

Causes differ according to age; temporal arteritis is very uncommon in patients under ~55 years, for example. Migraine may be associated with classic features (➔ *OHCM* 10e, Chapter 10). Remember to enquire about the combined OCP—may exacerbate migraine. 'Tension' headaches predominate.

Causes in adults include

- 'Tension' headache (very common; usually recurrent and stereotyped).
- Migraine. Although common, many patients who believe they have 'migraine' probably have 'tension' headaches. Classic migraine predominantly affects adolescents and young adults.
- Cluster headaches.
- As part of a generalized viral illness, e.g. 'flu'.
- Causes of ↑ ICP (➔ *OHCM* 10e, Chapter 10).
- Acute infective meningitis (bacterial, viral most commonly).
- Encephalitis (most commonly viral, e.g. herpes simplex).
- Intracerebral haemorrhage.
- Post-traumatic (common).
- Intracerebral tumour (1° or 2°, benign or malignant).
- Acute SAH.
- Subdural haematoma.
- Acute glaucoma.
- Acute sinusitis.
- Rubeosis iridis (2° glaucoma in patients with advanced diabetic eye disease).
- TN.
- Referred pain, e.g. from dental caries or sepsis.
- Arterial hypertension; malignant or accelerated phase; essential hypertension is rarely the cause of headache.
- TA. ►► Visual loss preventable with prompt corticosteroid therapy (➔ *OHCM* 10e, Chapter 10).
- Venous sinus thrombosis.
- Benign intracranial hypertension (mimics intracerebral tumour).
- Pneumonia caused by *Mycoplasma pneumoniae* may be associated with headache (meningoencephalitis).
- Nocturnal hypoglycaemia (often unrecognized) may cause morning headaches in patients with insulin-treated DM.
- Analgesia-withdrawal headache (➔ *OHCM* 10e, Chapter 10).
- Hangover following alcohol excess.
- Otitis media.
- Chronic hypercalcaemia (rare).

Investigations

- ESR (▶▶ TA—exclude with urgency).
- CRP.
- FBC.
- U&E.
- Throat swabs.
- Blood cultures (if febrile).
- LP (➔ Lumbar puncture, pp. 584–9).
- Skull X-ray (SXR) ± cervical spine X-ray.
- Sinus X-rays (may be local tenderness in sinusitis).
- Cranial CT (➔ Computed tomography, pp. 598–600).
- CXR (cerebral metastases from bronchogenic carcinoma).
- Urinalysis.
- Intraocular pressure measurement and refraction.
- Cerebral angiography (if aneurysm or AVM).
- Serum Ca^{2+}.

➔ *OHCM* 10e, p. 64, pp. 456–7.

Heart sounds and murmurs

Auscultation of the heart should be conducted over several cardiac cycles. Heart sounds and murmurs are traditionally assessed at the apex, *lower left sternal edge, aortic area*, and *pulmonary area*, but they may radiate into other regions such as the axilla or carotid arteries. The carotid pulse should be palpated simultaneously in order to time cardiac events. The following should be identified:

- First (S1) and second (S2) heart sounds.
- Added heart sounds such as third (S3) or fourth (S4) heart sounds, opening snaps, ejection clicks, and prosthetic sounds.
- Murmurs, including location, intensity, and characteristics.

The *first heart sound* is produced by closure of the mitral and tricuspid valves. It is best heard at the apex and is timed just prior to the carotid pulse. The *second heart sound* is caused by closure of the aortic (A2) and pulmonary (P2) valves and is heard just after carotid pulsation. Closure of the pulmonary valve is slightly delayed relative to the aortic valve and so the second heart sound is normally split. This split is exaggerated by inspiration (see Table 1.7).

Normal and abnormal heart sounds are shown in Table 1.7.

The *third heart sound* is heard just after S2 and arises as a consequence of rapid ventricular filling and volume overload. The *fourth heart sound* occurs just before S1 and is caused by atrial contraction against a stiff ventricle or pressure overload. Abnormal valves may cause extra heart sounds on opening, e.g. an opening snap or ejection click. The heart sounds generated by artificial valve closure are referred to as prosthetic heart sounds. These should be crisp, not muffled (see Table 1.8).

Murmurs may be graded according to the following criteria

1. Very soft (just audible under optimal conditions).
2. Soft.
3. Moderate (easily heard with a stethoscope).
4. Loud ± palpable thrill.
5. Very loud/palpable thrill.
6. Heard without a stethoscope/palpable thrill.

Innocent murmurs are generated by turbulent flow such as in high cardiac output states, e.g. pregnancy, fever, anaemia, and thyrotoxicosis. They have the following characteristics:

- No accompanying thrill.
- Never > grade 3.
- Systolic.
- Maximal at the left sternal edge.
- Normal heart sounds.
- Normal pulses, ECG, and CXR.

Systolic murmurs are synchronous with the carotid pulse and caused by

- Abnormal regurgitation through a structure that is normally closed in systole, e.g. AV valve, septum (pansystolic).
- Normal systolic flow through a narrowed or stenosed valve, e.g. aortic valve, pulmonary valve (ejection systolic).

Table 1.7 Normal and abnormal heart sounds

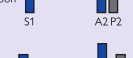
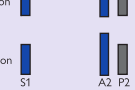
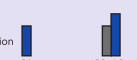
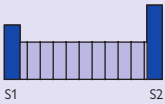
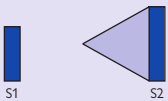
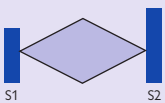
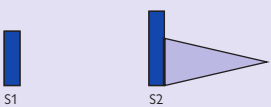
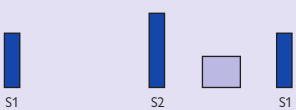
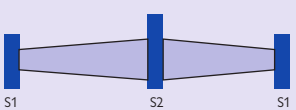
Description	Diagram	Differential diagnosis
Normal		Normal
Loud S1		Hyperdynamic circulation–anaemia, fever, thyrotoxicosis Mitral stenosis Left atrial myxoma
Soft S1		Low cardiac output Heart failure Tachycardia Mitral regurgitation Chronic obstructive pulmonary syndrome
		Systemic hypertension Dilated aortic root
Loud S2 (A2)		Aortic stenosis Cardiac failure
Soft S2 (A2)		Pulmonary stenosis
Soft S2 (P2)		Pulmonary hypertension
Loud S2 (P2)		Normal physiological splitting exaggerated in: right bundle branch block, pulmonary stenosis, pulmonary hypertension
		
Normal split S2		Atrial septal defect
		
Fixed splitting S2		Left bundle branch block Systemic hypertension Aortic stenosis
Reversed splitting S2		

Table 1.8 Heart murmurs

Pansystolic murmur		Mitral regurgitation Tricuspid regurgitation VSD
Late systolic murmur		Mitral valve prolapse Hypertrophic obstructive cardiomyopathy Aortic coarctation
Ejection systolic murmur		Aortic stenosis Pulmonary stenosis
Early diastolic murmur		Aortic regurgitation Pulmonary regurgitation
Mid-diastolic murmur		Mitral stenosis Tricuspid stenosis
Mixed murmur		Mixed valvular heart disease Patent ductus arteriosus AVMs Collateral circulations

Diastolic murmurs are audible after the carotid pulse and arise from

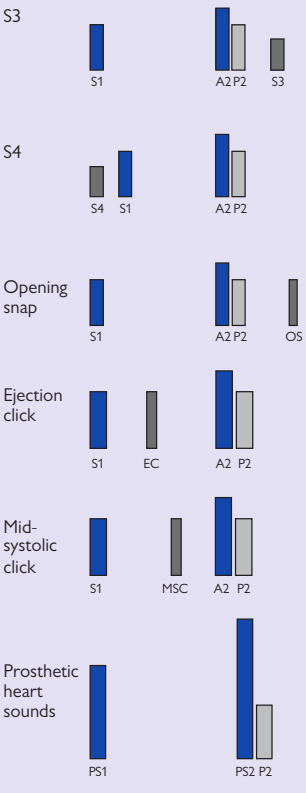
- Incompetence of the cardiac outflow valves, e.g. aortic or pulmonary valves.
- Narrowing of the cardiac inflow valves, e.g. mitral or tricuspid valves.

Mixed murmurs (systolic and diastolic) arise from

- Mixed valvular disease (stenosis and regurgitation).
- Patent ductus arteriosus.

Murmurs arising from left heart structures are accentuated in expiration, whereas right heart murmurs are augmented in inspiration (see Table 1.9).

Table 1.9 Added heart sounds



Hepatomegaly

Measure the liver edge below the (right) costal margin after percussing out the upper and lower borders. Bruits may be heard in hepatoma and a friction rub may occur with malignant deposits. Other signs may suggest the underlying diagnosis (➔ Pitfalls below).

Common causes

- CCF.
- Malignant deposits.
- Hepatitis/cirrhosis (usually alcoholic or infectious, e.g. Epstein–Barr virus (EBV), viral hepatitis).

Foreign residence?

If so, consider amoebic and hydatid cysts, schistosomiasis, and malaria.

Investigations

- FBC, film, LDH (leukaemia, lymphoma).
- ESR.
- Virology (EBV, CMV, and hepatitis A, B, and C antibody serology).
- LFTs—transaminases.
- Serum albumin.
- Prothrombin time (PT) (hepatocellular damage).
- γ-glutamyl transpeptidase (GGT), MCV (alcohol).
- ALP (obstructive causes; malignant deposits if isolated ↑).
- Serum Igs may be polyclonal ↑ in immunoglobulin G (IgG) (autoimmune hepatitis), immunoglobulin A (IgA) (alcoholic liver disease), or immunoglobulin M (IgM) (PBC).
- Serum protein electrophoresis (myeloma, amyloid).
- Reticulocytes, bilirubin (if ↑, suggests haemolysis).
- Haemoglobinopathy screen (thalassaemia/sickle disorders).
- USS to assess liver texture, splenomegaly, lymphadenopathy.
- CXR and cardiac investigations (cardiomyopathies, sarcoid).
- α-fetoprotein (AFP) (primary hepatocellular carcinoma).
- Serum ferritin, transferrin saturation, DNA analysis (haemochromatosis).
- Mitochondrial antibodies and autoimmune markers, e.g. ANA (autoimmune hepatitis), ANCA (primary sclerosing cholangitis).
- Caeruloplasmin, urinary copper (Wilson's disease).
- α1-antitrypsin (α1-antitrypsin deficiency).
- Porphyria screen.

Pitfalls

- Hepatomegaly is a common sign but may not necessarily implicate liver pathology.
- End-stage cirrhosis may commonly present with a small, shrunken liver.

➔ *OHCM* 10e, p. 63, p. 604.

Herpes zoster

The pattern of the eruption varies from mild to dense with the involvement of several dermatomes. Complications may occur if involvement of the eye, motor nerves, and autonomic nerves (bladder), or when the disease presents as an encephalomyelitis or purpura fulminans.

►► In the immunocompromised host, zoster is more likely both to occur and to disseminate.

Investigations

- Confirm the diagnosis by isolation of the virus from the vesicular fluid.
- Consider underlying disorders if recurrent or severe attacks.
- Look for lymphadenopathy (Hodgkin's or other lymphoma).
- FBC, blood film, LDH (↑ in lymphoma).
- Serum protein electrophoresis (myeloma, amyloid).
- Serology for HIV (zoster is common in adult HIV individuals).
- Immunodeficiency work-up.

Pitfalls

The rash is not always unilateral—it may be bilateral.

➔ *OHCM* 10e, p. 462.

Hyperlipidaemia

Abnormalities of lipid metabolism are common in Western societies. Populations with high levels of cholesterol have high rates of vascular morbidity, especially cardiovascular disease (CVD), and premature death. Vascular risk can be estimated from published risk tables or calculators.

Various classifications of hyperlipidaemia exist, each with a characteristic lipid profile. Many patients with lipid disorders have cutaneous markers, which identify to a certain extent the type of lipid abnormality.

Clinical features

Lipid abnormalities may cause dermatological manifestations

- Grey-yellow plaques or xanthomata in tendons, especially the forearm and Achilles. Usually indicative of elevated low-density lipoprotein (LDL) cholesterol.
- Corneal arcus, a thin white rim around the iris—whilst this is common in the elderly, it is not a sign of ↑ LDL, except in the under 40s.
- Yellow, fatty deposits or xanthelasmata around the eyelids—associated with elevated LDL, these painless, non-tender plaques are common in the elderly.
- Yellow streaks in palmar creases—palmar xanthomata are associated with IDL cholesterol.
- Plaques over tibial tuberosities and elbows—tubero-eruptive xanthomata. Often seen with hepatosplenomegaly with elevated triglycerides.
- Eruptive xanthomata—in severe triglyceridaemia, associated with pancreatitis and hepatomegaly.

Hyperlipidaemia may be 2° to drugs such as corticosteroids, oestrogens, and progestogens, as well as a range of conditions such as hypothyroidism, myeloma, and alcoholism, each of which may be associated with specific clinical signs.

Hypertension

Blood pressure (BP) measurements are graded into a number of categories by the British Hypertension Society (see Box 1.1):

Box 1.1 British Hypertension Society grading of hypertension

Optimal blood pressure	<120/80
Normal blood pressure	<130/85
High-normal blood pressure	130–139/85–89
Grade 1 hypertension (mild)	140–159/90–99
Grade 2 hypertension (moderate)	160–179/100–109
Grade 3 hypertension (severe)	≥180/110

Hypertension should not be diagnosed on the basis of a single BP reading. Unless urgent treatment is required, e.g. malignant hypertension, the BP should be rechecked over a number of weeks to confirm the presence of sustained hypertension.

Causes

Remember that the cause of hypertension in most (95%) cases is unknown ('essential' hypertension). One of the following identifiable causes can be found in the remaining 5%:

- Renal disease, e.g. polycystic kidney disease.
- Renovascular disease, e.g. renal artery stenosis (RAS).
- Endocrine disease, e.g. Cushing's syndrome, Conn's syndrome, phaeochromocytoma, acromegaly.
- Coarctation of the aorta.
- Drugs, e.g. NSAIDs, OCP, steroids, erythropoietin (Epo), sympathomimetics, liquorice.
- Pregnancy, e.g. pre-eclampsia, eclampsia.

Routine investigation

The investigation of hypertensive patients has the following aims

- To confirm the presence and severity of hypertension.
- To assess overall cardiovascular risk.
- To identify target organ damage.
- To identify 2° causes (where present).

Routine investigations should include

- Urinalysis (protein, blood, glucose).
- U&E.
- Plasma glucose (ideally fasted).
- Lipid profile (ideally fasted).
- 12-lead ECG.

CXR, urine microscopy and culture, and echocardiography are not required routinely but should be considered where indicated by your initial assessment and investigation of the patient. The use of 24h ambulatory BP monitoring is often useful where clinic readings are thought to be unreliable because of 'white coat' hypertension.

Further investigation

Where more detailed assessment is required (for instance, to rule out a 2° cause or to identify end-organ damage), the following investigations may be appropriate:

Renal investigations

- Renal USS (to assess overall renal morphology).
- Renal artery Doppler studies (for RAS).
- Renal artery magnetic resonance (MR) imaging (for RAS).
- Captopril renogram (for RAS).
- Renal angiography (for RAS).
- Renal vein renin measurements (for Conn's syndrome).

Endocrine investigations

- Renin and aldosterone studies for Conn's syndrome (consult your local endocrine laboratory).
- Investigations for Cushing's syndrome.
- Investigations for acromegaly.
- Urinary catecholamine (and metabolite) excretion.

Further reading

Williams B, Poulter NR, Brown MJ, *et al*. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV. *J Hum Hypertens* 2004; **18**: 139–85.

Incontinence: faecal

➔ Alteration of bowel habit, p. 9; ➔ Constipation, pp. 29–30; ➔ Diarrhoea, pp. 32–3.

Causes include

- Any cause of diarrhoea (➔ *OHCM* 10e, Chapter 6).
- Overflow diarrhoea from severe constipation.
- IBD (acute or chronic).
- Coeliac disease (diarrhoea is a variable feature).
- Infectious diarrhoea (➔ *OHCM* 10e, Chapter 1).
- Hyperthyroidism (may cause diarrhoea; rare cause of incontinence).
- Carcinoma of the colon (stricture).
- Diverticular disease of the colon (acute attack, chronic stricture).
- Neurological (multiple CVAs, MS, spina bifida, post-childbirth neuropathy) may often be associated with sphincter disturbances.
- Drugs, e.g. laxatives, orlistat (causes fat malabsorption).
- Causes of steatorrhoea (➔ *OHCM* 10e, Chapter 6).
- Intestinal hurry, e.g. post-gastrectomy (➔ *OHCM* 10e, Chapter 6).
- Diabetic diarrhoea (autonomic neuropathy—rare; diagnosis of exclusion but may cause nocturnal faecal incontinence).
- VIPoma (very rare).

Investigations

Non-invasive tests

- Stool cultures (ova cysts, parasites). *Note: Clostridium difficile*—relatively common in patients who have received recent antibiotic therapy.
- FBC (anaemia, especially iron deficiency).
- CRP.
- ESR.
- U&E.
- TFTs.

Imaging

- Pelvic/abdominal X-ray.
- Barium enema.
- CT abdomen.

Procedures

- Colonoscopy.
- Sigmoidoscopy ± biopsy.

➔ *OHCM* 10e, p. 58.

Incontinence: urinary

Anuria, p. 14.

Consider

- Common causes of polyuria (*OHCM* 10e, Chapter 7); these may present as, or aggravate, urinary incontinence.
- Acute or chronic confusional state (common; loss of voluntary sphincter control).
- UTI (very common—always exclude).
- Drug-induced, e.g. thiazide or loop diuretics; α-adrenergic blockade, e.g. doxazosin (uncommon).
- Psychological, e.g. severe depression.
- Immobility, e.g. PD (Shy–Drager syndrome is uncommon).
- Other causes of autonomic neuropathy (*OHCM* 10e, Chapter 10).
- Detrusor muscle instability.
- Urethral incompetence.
- Stool impaction.
- Spinal cord compression.
- Tabes dorsalis.

Investigations

- U&E.
- Urinalysis for blood, protein, glucose, nitrates, and nitrites.
- MSU for culture and sensitivity (C&S).
- Plasma glucose (if glycosuria).
- Serum Ca^{2+}.

In selected patients, consider referral to urology or gynaecology services for consideration of:

- Bladder manometry studies.
- Post-voiding USS of the bladder.
- Pelvic imaging, e.g. CT scan.

OHCM 10e, pp. 648–9.

Indigestion

This term is often loosely used by patients to describe a variety of symptoms. These are often regarded as representing relatively minor, and usually intermittent, pathology. However, serious pathology, e.g. carcinoma of the stomach, may present as a vague complaint of 'indigestion'. The symptoms may be retrosternal or abdominal. A detailed history is essential, focusing on features that raise the probability of serious pathology, e.g. dysphagia and weight loss.

Examination

Examination should include a search for the following signs, particularly in the middle-aged and elderly patients:

- Anaemia (especially iron deficiency—common).
- Ascites.
- Troisier's sign (malignant involvement of the left supraclavicular lymph nodes due to carcinoma of the stomach—rare).

Note: the presence of associated pathologies, e.g. pernicious anaemia (➔ *OHCM* 10e, Chapter 8)—↑ risk of stomach cancer—will alter the threshold for more detailed expert investigation. Carcinoma of the stomach is commoner in Japanese.

Peptic ulceration may have classic elements that point to the diagnosis. Non-ulcer dyspepsia is very common and is often treated empirically with antacids, H_2 receptor antagonists, or H^+ pump inhibitor drugs. The clinical challenge is to identify the patient for whom more detailed, and often invasive, investigation is indicated.

Alternative causes, e.g. cardiac ischaemia, should be considered in the differential diagnosis; similarities of the symptoms between cardiac and upper GI disorders are well recognized and sometimes pose considerable diagnostic difficulties.

Causes include

- Oesophageal acid reflux.
- Hiatus hernia.
- Inflammatory disease.
- Peptic ulcer disease of the duodenum or stomach.
- Biliary colic (usually distinctive clinical features).
- Malignancy of the oesophagus, stomach, or rarely small intestine.
- Cardiac symptoms, usually ischaemia.
- IBS.
- Symptoms arising from other structures within the chest or abdomen.

Investigations

- FBC.
- U&E.
- ESR.
- Upper GI endoscopy ± tissue biopsy.
- LFTs.
- CK if MI/acute coronary syndrome (ACS) suspected.
- Troponin (T or I) if MI/ACS suspected.

- Serum amylase (normal in chronic pancreatitis; may be ↑ by a duodenal ulcer eroding the posterior wall).
- Barium swallow and meal (for oesophageal disease).
- CLO test for *Helicobacter pylori*.
- Urea ^{13}C breath test for *H. pylori*.
- USS of the biliary tract (➔ Ultrasound, p. 802).
- Cholecystogram.

If diagnosis remains uncertain, consider

- CT abdomen (discuss with a radiologist).
- Serum gastrin (Zollinger–Ellison syndrome, ➔ *OHCM* 10e, p. 716).
- 24h ambulatory oesophageal pH monitoring.
- Oesophageal manometry (oesophageal motility disorders).

Infective endocarditis signs

Infective endocarditis is characterized by infection of the endocardial surface of the heart. The left heart valves are the most commonly affected, but the right heart valves and congenital heart lesions, such as VSDs, may also become infected. Vegetations (composed of the organism, white cells, platelets, and fibrous tissue) are formed at the site of infection. They give rise to periodic septicaemia and may embolize to other parts of the body. There is gradual destruction of the valve with ↑ valvular dysfunction, regurgitation, and heart failure.

Clinical features

- Pyrexia (low-grade or swinging).
- Pale conjunctivae suggestive of anaemia (of chronic disease).
- Clubbing (chronic low-grade infection).
- Cardiac murmur (new or changing).
- Left or right heart failure.
- Splenomegaly (friction rub if splenic infarction is present).
- Microscopic haematuria (on urinalysis).

Embolic phenomena

Embolic phenomena are common and produce clinical signs classically associated with infective endocarditis:

- Splinter haemorrhages (>5, sited in the proximal finger and toenail beds).
- Janeway lesions (palmar macular spots).
- Osler's nodes (painful nodules on the palmar surface of the fingers or toes).
- Roth spots (retinal haemorrhages).
- Conjunctival haemorrhages.
- Microvascular infarction (in the distal limbs).

Further reading

Prendergast BD. Diagnostic criteria and problems in infective endocarditis. *Heart* 2004; **90**: 611–13.

Task Force on Infective Endocarditis of the ESC. Guidelines on prevention, diagnosis and treatment of infective endocarditis. *Eur Heart J* 2004; **25**: 267–76.