

Kumar and Clark's
**CASES IN
CLINICAL MEDICINE**

THIRD EDITION

Edited by
Parveen Kumar
Michael Clark

POCKET ESSENTIALS



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KUMAR & CLARK'S

CASES IN CLINICAL
MEDICINE

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KUMAR & CLARK'S

CASES IN CLINICAL MEDICINE

3rd edition

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Contents

Preface xi

Acknowledgements xiii

1	Infectious Diseases	1
	Pyrexia of unknown origin (PUO)	1
	Septicaemia	4
	Meningococcal meningitis and septicaemia	7
	Pseudomembranous colitis	9
	Food poisoning: <i>E. coli</i> 0157	11
	Typhoid	13
	The returning traveller	14
	Shingles	16
	Epstein–Barr virus	18
2	Sexually Transmitted Infections	21
	HIV/AIDS	21
3	Nutrition	27
	Feeding the patient	27
4	Gastroenterology	31
	Vomiting	31
	Hiccups	33
	Weight loss	34
	Dysphagia	35
	Constipation	36
	Diarrhoea	37
	Abdominal pain	43
	Gastro-oesophageal reflux disease (GORD)	45
	Barrett's oesophagus	46
	Peptic ulcer disease	46
	Iron deficiency anaemia	50
	Rectal bleeding	52
	Family history of colon cancer	53
	Functional bowel disease	55
5	Liver and Biliary Tract Disorders	57
	Abnormal liver biochemistry	57
	Jaundice	59
	Acute liver disease	63
	Ascites	64
	Haematemesis and melaena	66
	Liver failure	70
	Excess alcohol use	71
	Cholecystitis	73

6	Haematology and Oncology	77
	Microcytic and macrocytic anaemia	77
	Haemolytic anaemia	83
	Sickle-cell disease	86
	Types of sickle-cell disease	89
	Elevated haemoglobin (polycythaemia)	92
	Elevated white blood cell count	97
	Elevated platelet count	98
	Glucose-6-phosphate dehydrogenase deficiency	100
	Bleeding disorders	105
	Disseminated intravascular coagulation (DIC)	109
	Platelet disorders	112
	Thrombosis	116
	Splenomegaly, splenectomy and hyposplenism	121
	Blood transfusion	125
	Haematological oncology	131
	Anaemia in rheumatoid arthritis	140
	Anaemia in cancer	142
	Infection/sepsis	144
7	Care of the Elderly	149
	Blackouts	149
	Falls in the elderly	151
	Delirium	153
	Dementia	156
	Depression	159
	Non-specific presentation of illness in the elderly	161
	Appropriate assessment scales	163
	Stroke	163
	Heart disease in the elderly	172
	Transient ischaemic attack	174
	Hypothermia	175
	Pressure ulcers	177
	Urinary tract infection and incontinence	179
	Arteritis	181
	Acute hot joint	182
	Parkinson's disease	184
	Drug treatment in older people/drug treatment as a cause of illness and admission to hospital	186
	Drugs as a cause of illness and delayed discharge	186
	Do not attempt resuscitation (DNAR) decision-making	188
8	Rheumatology	191
	Osteoarthritis (OA)	191
	Rheumatoid arthritis (RA)	197
	SLE and vasculitis	200
	Acute autoimmune rheumatic disease	202
	Thrombosis and the anti-phospholipid syndrome	206
	Crystal arthritis	209

Polymyalgia rheumatica/cranial arteritis	212
Acute back pain	213
Severe back pain/osteoporosis	215
Osteomyelitis	218
Septic arthritis	219

9 Kidney and Urinary Tract Disease 223

Presentation of kidney and urinary tract disease	223
Fluid balance and electrolytes: assessing fluid status	223
Fluid balance and electrolytes: sodium problems	227
Patient stopped passing urine	230
Acute heart failure	233
Hyperkalaemia	238
The acidotic patient	241
Acute kidney injury	245
Chronic kidney disease	246
Multisystem vasculitis/acute glomerulonephritis	251
Intercurrent illness in dialysis and transplant patients	254
Nephrotic syndrome	257
Haematuria without albuminuria	259
Urinary tract infection (UTI)	260
Renal and ureteric colic	262

10 Cardiology 265

Syncope	265
A clinical approach to patients with tachycardia	268
Atrial fibrillation	274
Bradycardia and pacing	277
Cardiac arrest and basic life support	280
Chest pain and acute coronary syndromes	284
Thrombolysis	286
Acute myocardial ischaemia – who needs acute intervention?	291
Cardiogenic shock	292
Right ventricular infarction	295
Heart failure following an MI	297
Post-infarction arrhythmias and heart block	298
Myocardial infarction – secondary prevention	301
Heart failure recognition and acute management	303
Valvular heart disease	306
Infective endocarditis	309
Pulmonary hypertension	312
Cardiomyopathies	315
Hypertension (HT)	317
The swollen/painful leg	323

11 Respiratory Disorders 325

Acute breathlessness	325
Cough	326
Breathlessness and wheeze	328
Hyperventilation	332

Haemoptysis	333
Chest pain	336
Respiratory failure	338
COPD – acute exacerbation	344
Pneumonia	350
Lung abscess	357
Tuberculosis	358
Pleural effusion	363
Pulmonary embolism (and deep vein thrombosis)	366
Pneumothorax	369
Carcinoma of the bronchus	372
Sarcoidosis	378

12	ITU	383
	Shock	383
	Acute lung injury/Acute Respiratory Distress Syndrome (ARDS)	390

13	Poisoning	395
	Self-poisoning	395
	Paracetamol (acetaminophen) poisoning	398
	Salicylate overdose	402
	Cocaine	404
	Gammahydroxybutyric acid (GHB)	407
	Insect stings and bites	408
	Anaphylactic shock	408

14	Endocrinology and Diabetes	411
	Diabetes mellitus	411
	Diabetic ketoacidosis (DKA)	413
	Hyperosmolar hyperglycaemic state	418
	Hypoglycaemic coma	420
	Sick diabetic patient	422
	Management of new type 2 diabetic presenting for surgery	424
	Urgent surgery in patients with diabetes	426
	Diabetic foot	427
	Diabetes in pregnancy	429
	Cushing's syndrome	430
	Hyperthyroidism	432
	Amiodarone and thyroid function	439
	Hypothyroidism	440
	Addison's disease	442
	Patients on steroids for surgery	444
	Hypercalcaemia	446
	Severe hypercalcaemia	448
	Hypocalcaemia	449
	Phaeochromocytoma (catecholamine crisis)	452
	Hypopituitarism	454
	Diabetes insipidus	457
	Syndrome of inappropriate anti-diuretic hormone (SIADH)	459

15	Neurology	461
	Diplopia	461
	Loss of vision	466
	Bell's palsy	468
	Vertigo	469
	Stroke	472
	Subdural haemorrhage	477
	Parkinson's disease	478
	Multiple sclerosis (MS)	480
	Encephalitis	482
	Falls	485
	Traumatic brain injury	486
	General management of traumatic injuries	487
	Severe brain injury	489
	Meningitis	491
	Fits and faints	496
	Difficulty walking	499
	Headaches	501
	Movement disorders	504
	Guillain–Barré syndrome	506
	Spinal cord compression	507
16	Psychiatry	509
	Delirium	509
	Drugs and poisons as causes of delirium	513
	Drugs causing delirium	513
	Dementia	516
	Delirium tremens (DT)	519
	Depression	522
	Suicide and deliberate self-harm (DSH)	527
	Acute anxiety	532
	Opiate dependence	534
	The disturbed patient	537
17	Dermatology	541
	A swollen red leg	541
	Erythema nodosum	543
	Urticaria and angio-oedema	545
	Sun-induced rash	548
	Generalised rash or eruption	550
	Pruritus	551
	Cutaneous adverse drug reactions (ADR)	553
	HIV and the skin	559

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Preface

Medical education has changed enormously over the last two decades. From the traditional didactic, lecture-based approach we have moved to an environment where the student takes greater responsibility for their study through self-directed learning and small group interactions. Various curriculum models have been employed in medical schools, incorporating different teaching methodologies such as problem-based, task-based and outcome-based learning. Fundamental to all medical training is that the practice of medicine should be evidence-based as far as is possible. This requires a sound knowledge base and a constant desire to keep up-to-date.

We all, of course, learn in different ways, but what is essential is that there is a defined structure which can guide us to learn effectively, efficiently and sensibly. Getting the right emphasis will help senior medical students and junior doctors define problems correctly and instigate appropriate management and treatment in a clinical setting.

‘Learning how to learn’ has become quite an art, beloved of all medical educationalists. However, there are basic rules that have to be absorbed prior to being able to ‘drive’ one’s own learning effectively. The plethora of facts a doctor needs to know in order to practise medicine efficiently needs to be broken down into easily assimilated chunks and presented in the context of a clinical problem.

Over the last decade, problem-based learning (PBL) has become a more formalised approach to medical education. The Maastricht seven-step method of PBL gives a helpful structure to tackling a clinical problem:

1. identify and clarify unfamiliar terms
2. define the problem(s)
3. brainstorm with a scribe recording the discussion
4. ‘sift and sort’ to review steps 2 and 3
5. formulate learning objectives
6. engage in private study
7. come back to the group to share what has been learned.

The objective is to come up with an evidence-based solution to the problems set, with the tutor checking the outcome. The problem is usually focused around a clinical case and stimulates the learner to consult the full range of learning resources available to them (libraries, textbooks, journals, online and digital sources). It encourages students to be self-directed in their learning, think critically, and work in a team to solve the problem themselves in lively, informal and interactive sessions.

Our book is designed to support this approach to clinically contextualised learning. In our first edition we set out to formulate an approach to what was then called ‘service-based learning’, pioneered by Professor Janet Grant at the Open University Centre for Education in Medicine in response to the General Medical Council’s aim to create an MRCP-level guide to learning on the job. Following research into clinical problem solving, students expressed their wish to have graded clinical experiences, the ability

to assess their own learning, and to have on-the-spot performance feedback.

In the first edition we used clinical cases where the histories of patients and their investigations were gradually revealed as time progressed and bits of data were added to the scenario, rather like a detective story! These cases were based on the real-life challenges commonly presenting in a hospital setting. All students will experience these when they encounter patients, and will have to sift through their knowledge to find facts that are applicable to the case in hand.

We included self-assessment questions in the previous editions of the book, but as these can be found elsewhere, we have removed them this edition and instead have devoted the space to more clinical scenarios to test your knowledge and problem solving abilities. The material has been completely updated and we have added more figures and tables to further facilitate your learning.

We hope we have managed to present this in a fun way and stimulate you to consult the bigger texts such as *Kumar and Clark's Clinical Medicine* or our new handbook *Kumar & Clark's Medical Management and Therapeutics*. These books have been written in response to your requests and we hope you will continue to inform us of your needs.

We wish you a happy read!

Parveen Kumar and Michael Clark

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We would like to thank the original contributors:

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PYREXIA OF UNKNOWN ORIGIN (PUO)

Pyrexia of unknown origin (sometimes called fever of unknown origin, FUO) is best defined as a fever persisting for more than 2 weeks with no clear diagnosis despite intelligent and intensive investigation.

Not all cases of PUO are due to infection. In recent-onset PUO, approximately two-thirds of cases are due to infection, compared with only about one-third of cases with long-standing PUO. Other causes include malignancy and autoimmune rheumatic disorders (Table 1.1).

Case history

A 25-year-old male is seen in the A&E department, at the request of his doctor, with a history of fever, anorexia and malaise. He had returned the previous week from a month's backpacking trip around India, where he had lost 5 kg in weight. The casualty officer asks you to see this patient with PUO. The preliminary blood investigations by the GP were normal.

On examination, the patient was found to be febrile with a temperature of 39.5°C. He had no lymphadenopathy or pallor of mucous membranes.

BP 110/70; pulse 90; heart sounds normal.

Chest: clinically clear.

Examination of abdomen: slight generalised tenderness. Liver, kidneys and spleen not palpable. Examination of CNS: unremarkable.

Where would you manage this patient?

Admit to a MAU side room until an infectious aetiology has been ruled out.

What questions should you specifically ask when you see a patient with PUO (in addition to routine questions)?

- Full travel history, including exactly where patient has been and the type of accommodation stayed in
- Vaccination/prophylaxis history
- Contact with animals/sick people
- Occupation: exactly what does the patient do?
- Water exposure: occupational/recreational
- Food history: eating shellfish, drinking dirty water, reheated/raw foods
- Risk behaviour: IV drug usage, unprotected sex
- Factors that might predispose to infection.

Table 1.1 Causes of PUO

Infections (see below)
 Neoplasms, especially lymphomas, renal cell carcinoma
 Autoimmune rheumatic disease
 Vasculitides, e.g. giant cell arteritis
 Others, e.g. granulomatous disease, drug reactions, factitious

Infective causes**General**

Abscesses, e.g. liver, abdomen, pelvis, ear, sinus or dental infection
 Infective endocarditis
 Urinary tract infection

Specific**Bacterial**

Mycobacterium tuberculosis
Salmonella typhi or *S. paratyphi*
Brucella spp.
 Leptospirosis
 Lyme disease

Viral

Epstein–Barr
 Hepatitis
 Cytomegalovirus
 HIV
 Dengue fever

Protozoal diseases

Malaria
 Amoebiasis
 Leishmaniasis
 Toxoplasmosis
 Trypanosomiasis

Rickettsial diseases

Typhus
 Q fever

Chlamydophila

Psittacosis

What initial investigations should you perform in a patient presenting with PUO?

Perform minimally invasive tests before highly invasive and expensive ones. It is always worth repeating previously performed tests (see Investigations box).

Investigations for a PUO

- FBC
- CRP / ESR
- U&Es

Investigations for a PUO—cont'd

- Liver biochemistry
- Blood cultures – repeated
- Urine analysis and microscopy, culture and sensitivity
- CXR
- Sputum (if producing any) for microscopy, culture and sensitivity, and for acid-fast bacilli
- Stools for ova, cysts and parasites and culture and sensitivity
- Store serum for future serological tests if required
- Wounds: take swabs for culture
- Screen for autoimmune rheumatic disorders
- Additional investigations in this man because of travel abroad: thick and thin blood films for malaria

Results in this patient

- WCC: slightly raised at $12\,000 \times 10^9/L$
- ALT: 92 iu/L (normal range 5–40 iu/L)
- Alkaline phosphatase: 190 iu/L (normal range 25–115 iu/L)
- All other initial investigations were normal.

What should you do now?

- Recheck his history of travel
- Recheck his risk factors for hepatitis and HIV
- Send blood for viral markers for hepatitis
- Arrange a liver ultrasound.

The ultrasound shows a **liver abscess** in the right lobe and, in view of his travel, an amoebic abscess is a strong possibility. Fortunately, you had sent off an amoebic CFT sample and you ring the reference laboratory urgently. The test is positive (usually positive with an amoebic liver abscess).

Treatment

Treat with metronidazole 800 mg \times 3 daily for 10 days followed by diloxanide furoate 500 mg \times 3 daily for 10 days. Aspiration of the abscess is only required with failure of medical therapy.

Remember

- Take a careful history: *always repeat*
- Examine the patient thoroughly: *always repeat*
- Initial investigations often give a clue to the diagnosis: often need repeating
- Be patient and don't give antibiotics until diagnosis is made unless the patient is very sick
- Perform invasive and/or expensive investigations only when appropriate, e.g. echo, CT scan/MRI, bone marrow and culture, lymph node/liver biopsy.

- **Progress.** This man responded quickly to therapy with loss of pain, improvement in appetite and he became afebrile after 4 days. A repeat ultrasound 3 weeks later still showed a small residual cavity.

Further reading

WHO. Infectious diseases. http://www.who.int/topics/infectious_diseases/en

SEPTICAEMIA

Septicaemia and bacteraemia should be differentiated. In *bacteraemia* there is a transient presence of live organisms in the blood which do not cause symptoms; it can occur in healthy patients.

In *septicaemia* there are signs and symptoms of a systemic inflammatory response syndrome (SIRS) to a localized primary site of infection. SIRS is defined as the presence of two or more of: heart rate > 90/min; WCC > 12 × 10⁹/L or < 4 × 10⁹/L; a temperature > 38°C or < 36°C and a respiratory rate > 20/min or a PaCO₂ < 4.3 kPa (<32 mmHg).

Case history

A 70-year-old woman was admitted to hospital with fever, confusion and hypotension. She lived on her own and was unable to give a history.

On examination, she was clinically dehydrated, confused and had cold clammy peripheries. Pulse rate 108/min, respiratory rate 22/min.

She was also hypotensive with a BP 90/50 and had a temperature of 39°C.

Diagnosis: Septic shock.

What are the most common causes of septicaemia in patients presenting from the community?

The most common organisms isolated are *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and pyogenic streptococci – especially group A streptococci. *Neisseria meningitidis* should not be forgotten as a possible cause of community-acquired sepsis.

In hospital, coagulase-negative staphylococci can also cause sepsis in immunosuppressed patients with IV lines in situ. Wounds, the respiratory tract (especially in ventilated patients) and the urinary tract (in catheterised patients) are other sources of sepsis in hospitalised patients.

What factors predispose to septicaemia?

In both Gram-positive and Gram-negative septicaemia, impaired host defences, surgery or instrumentation (including intravenous cannulae, urinary catheters and mechanical ventilation) predispose to septicaemia (Table 1.2).

Table 1.2 Predisposing factors for septicaemia

Gram-negative sepsis	Gram-positive sepsis
Urinary tract infections	IV catheters
Hospital acquired pneumonia, especially ventilator associated	Skin/wound infections Bone and joint infections
Pre-existing abdominal sepsis, biliary tract infections	IV drug usage
Severe burns	Respiratory tract infections/ pneumonia
Obstetric or neonatal infections	Obstetric or neonatal infections
Meningococcal septicaemia	Meningitis, endocarditis

What is the differential diagnosis of septic shock?

Non-infective disorders, such as acute myocardial infarction, pulmonary embolism or drug reactions, must be excluded. Toxic shock (e.g. toxic shock syndrome) can also present in a similar manner.

What would be your initial management of this woman and what investigations would you do?

This patient required supportive therapy (e.g. fluid replacement) because she was dehydrated and oxygen was given and inotropes. Broad-spectrum antibiotics were started after blood and urine cultures had been taken. The antibiotic therapy varies according to local hospital policy and the likely focus of infection. This severely shocked patient was transferred to HDU/ITU (see p. 383).

Investigations

- FBC and differential
- U&Es, blood sugar, liver biochemistry
- ESR/CRP
- Blood cultures
- Blood gases
- Urine for microscopy, culture and sensitivity
- Sputum (if any produced) for microscopy, culture and sensitivity
- Swabs of any infected-looking lesions (including throat swab if throat appears inflamed)
- Pus (if present) for microscopy, culture and sensitivity
- High vaginal swab in women
- NAAT (nuclear acid amplification test)
- CXR
- ECG

If a *urinary tract infection* is thought to be the likely source, a broad-spectrum cephalosporin is often appropriate (e.g. cefuroxime) or a quinolone (e.g. ciprofloxacin).

If there is no obvious focus of infection, blind therapy must be broad spectrum and cover streptococci, staphylococci and coliforms.

Suitable choices are:

- A broad-spectrum cephalosporin such as IV cefuroxime or IV cefotaxime or IV ceftriaxone.
- Metronidazole should be added if an anaerobic infection is considered likely.
- A broad-spectrum penicillin with β -lactamase inhibitor (e.g. piperacillin/tazobactam). Gentamicin can be added if the patient is very ill.
- A carbapenem (e.g. imipenem, although this is a restricted antibiotic in many hospitals).

Remember

- If you give gentamicin, remember that you need to monitor serum levels. Combining it with a cephalosporin can potentiate its nephrotoxicity.
- Cefuroxime, ceftriaxone and cefotaxime have fairly good activity against staphylococci and streptococci, as well as against many Gram-negative rods; they have poor activity against *Pseudomonas* spp. Ceftazidime has poor activity against streptococci and staphylococci but excellent activity against *Pseudomonas* spp. and other Gram-negative organisms. No cephalosporins are active against *Enterococcus* spp.
- Cephalosporins are associated with *C. difficile* diarrhoea and should be avoided if possible.
- If a patient develops sepsis while in hospital it is possible that this is due to resistant organisms, e.g. methicillin-resistant *S. aureus* (MRSA) or resistant Gram-negative rods.
- If MRSA infection is considered likely and the patient is very sick, add IV vancomycin 1 g \times 2 per day (assuming normal renal function) given over at least 100 minutes while awaiting culture results.

A urine sample was obtained from this patient. Microscopy found it to contain 1000 WCC/mm³ and ++ bacteria.

- **Progress.** The patient had already been given IV cefuroxime and was continued on this. On admission she was also given a single dose of gentamicin. The following day both her urine and blood cultures grew an *E. coli* that was susceptible to cefuroxime and gentamicin but resistant to amoxicillin. She made a good recovery.

Remember

Many hospitals have specific guidelines for antibiotic usage: *always check* or get microbiological advice.

In your hospital, do you know the approximate percentage of organisms causing urinary tract infections that are susceptible to commonly used antibiotics?

In many areas, approximately 50% of *E. coli* causing urinary tract infection are resistant to amoxicillin and 20–30% are resistant to trimethoprim. More than 90% are susceptible to cefuroxime, ciprofloxacin and gentamicin. You need to know local resistance patterns.

MENINGOCOCCAL MENINGITIS AND SEPTICAEMIA

Case history

An 18-year-old woman is brought into A&E 'collapsed'. The previous day she had apparently been well apart from symptoms of a minor upper respiratory tract infection. She woke up feeling very unwell and asked her flat-mate to call the emergency doctor. The flat-mate noted that her friend had a couple of spots on her chest but by the time the doctor arrived she was developing a more widespread petechial rash. The emergency doctor transferred her immediately to hospital after giving her a single dose of benzylpenicillin.

The patient was febrile with a temperature of 38°C.

A petechial rash was present (Fig. 1.1).

The patient was hypotensive and shocked.

There was minimal neck stiffness.

What do you think is the most likely diagnosis?

This young woman has **fulminant meningococcaemia**, which has a worse prognosis than meningococcal meningitis and usually has an extremely rapid downhill course.

What should the immediate management be?

Take blood and throat cultures and then start antibiotics immediately. Give intravenous benzylpenicillin, initially 2.4 g 4-hourly *or* IV cefotaxime 2 g \times 6-hourly *or* IV ceftriaxone 2 g \times 2 daily for presumed meningococcal meningitis/septicaemia.



Figure 1.1 Meningococcal rash (from Fuller, Neurology Illustrated Colour Text, with permission).

Remember

The first doctor to see a patient suspected of having meningococcal septicaemia or meningitis should immediately give benzylpenicillin IM injection before immediate transfer to hospital.

What investigations should be performed?

Relevant investigations are shown in the box. Other causes of meningitis/septicaemia should be excluded.

Investigations

- FBC and differential
- U&E
- Liver function tests
- ESR or CRP
- Blood cultures: always before starting antibiotics
- Throat swab to look for meningococcal carriage
- Culture of petechial lesions is sometimes performed
- Lumbar puncture is not indicated in meningococcal septicaemia

Who should be informed and what further action should be taken?

The consultant (or his/her deputy) in charge of communicable disease control (CCDC) should be informed immediately by telephone if a clinical diagnosis of meningococcal disease is made. Formal notification should then be done in writing. Notification books should be kept on all wards. Rifampicin prophylaxis can then be arranged for any close contacts.

Contacts who should receive prophylaxis

- People who live in the same household as the case or who have lived there in the previous week
- Sexual partners
- Work fellows sharing a small office, i.e. an office for two
- Staff carrying out mouth-to-mouth resuscitation on the patient or 'specializing' the patient, especially in the first 24 h
- The patient herself at the end of her parenteral therapy
- School contacts if more than one case in a school.

Once the CCDC has been informed, he/she will usually arrange for chemoprophylaxis (Table 1.3), but might ask the hospital doctor to do this for the patient's relatives.

Remember

The patient should have rifampicin 600 mg \times 2 daily for 2 days after she has finished her parenteral antibiotics to eradicate carriage of *N. meningitidis* from her nasopharynx.

Table 1.3 Recommended chemoprophylaxis of meningococcal meningitis

Adults and children over 12 years Children 1–12 years Infants, 12 months	First choice Rifampicin 600 mg × 2 daily for 2 days 10 mg/kg × 2 daily for 2 days (maximum dose 600 mg × 2 daily for 2 days) 5 mg/kg × 2 daily for 2 days
Adults Children Pregnancy/breastfeeding mothers	Other options Ciprofloxacin 500 mg single dose Not recommended Not recommended
Adults Children, 12 years	Ceftriaxone 250 mg IM as a single dose 125 mg IM as a single dose

What should you tell people who are taking rifampicin prophylaxis?

- That it might interfere with the effectiveness of the oral contraceptive if they are taking this. Hence they should take additional contraceptive measures for the remainder of the cycle.
- That their secretions (e.g. tears) might turn orangey-pink and that their soft contact lenses will also be permanently stained unless they remove them!

Overall management

This patient was treated with intravenous ceftriaxone 2 g IV twice per day in the intensive care unit. After a stormy course she made a full recovery. There were no secondary cases.

Further reading

Quagliarello V. Dissemination of *Neisseria meningitidis*. *New England Journal of Medicine* 2011; **364**: 1573–1575.

PSEUDOMEMBRANOUS COLITIS

This is the condition caused by *Clostridium difficile*; a pseudomembrane is seen on sigmoidoscopy.

Case history

A 40-year-old man who had been on the intensive care unit for 3 weeks with a head injury following a road traffic accident developed severe diarrhoea. He was on a ventilator and currently was finishing a course of a third-generation parenteral cephalosporin for hospital acquired pneumonia. According to the nurses, one other patient on the ITU currently also has diarrhoea.

What other questions do you want to ask?

You would want to know:

- What the diarrhoea is like: are the stools liquid or bloody?
- How long has the patient been on broad-spectrum antibiotics?
- Has any other patient/member of the staff got diarrhoea? (One of the ITU nurses informs you that another patient did have loose stools and you need to ascertain if this is really the case and if there were any obvious reasons for this.)

What is your differential diagnosis?

This would include:

- Antibiotic-associated diarrhoea, particularly pseudomembranous colitis
- Diarrhoea due to enteral feeding
- Other bacterial causes, e.g. *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *E. coli* 0157; these are less likely because patient hasn't been eating but could occur as a result of cross-infection
- Viral gastroenteritis.

What investigations would you perform?

You would need to send a stool from the patient to the microbiology laboratory (and also from any other patient/staff member with diarrhoea) for microscopy, culture and sensitivity. If several patients/members of staff are affected, stools should also be sent to the virology department to look for a viral aetiology, e.g. small round viruses. In addition, you would specifically need to request an examination for *Clostridium difficile* (toxin) – the organism responsible for the toxin of pseudomembranous colitis. Do a sigmoidoscopy to look for the typical pseudomembrane seen in pseudomembranous colitis and to exclude inflammatory bowel disease by rectal biopsy.

The patient was thought, on clinical grounds, to have pseudomembranous colitis. This was later confirmed by the microbiology department, which found the stool to be positive for *C. difficile* toxin.

Remember

Culture of *C. difficile* itself in a stool is insufficient evidence that a patient has pseudomembranous colitis; only toxin-producing strains cause this.

How would you manage the patient?

The patient should be isolated in a side room if possible to prevent cross-infection. You need to ensure that the patient is adequately hydrated. In patients with antibiotic-associated diarrhoea, if it is at all possible, any broad-spectrum antibiotics that the patient is taking should be stopped. If it is not possible to stop all antibiotics, try and change to a narrow-spectrum agent (discuss with microbiology). Specific first-line therapy for pseudomembranous colitis is oral metronidazole 400 mg \times 3 for 7–10 days. Oral vancomycin 125–250 mg \times 4 for 7–10 days is used if no response to metronidazole. Fidaxomicin 200 mg is also effective.

Note: you do not need to do vancomycin levels in patients receiving oral vancomycin because it is not systemically absorbed.

Normally, metronidazole is tried first because there is a worry that use of oral vancomycin might predispose to the development of vancomycin-resistant enterococci in the gastrointestinal tract; in some parts of the world, enterococcal vancomycin resistance is becoming a major problem.

- **Progress.** This patient initially responded to metronidazole but after 8 days his diarrhoea returned (up to 30% of cases relapse) and he was switched to vancomycin, to which he responded.

He was eventually weaned from the ventilator and made a good physical recovery but with impaired cognitive function.

Remember

Prevention

Infection control relies on:

- Responsible use of antibiotics.
- Hygiene, which should involve all health workers, as well as patients and relatives.
- Washing hands thoroughly using soap and water is essential as alcohol disinfectants do not kill *C. difficile* spores.
- Hospital cleaning of surfaces should be performed regularly to try and reduce transmission from fomites.
- Isolation of patients with *C. difficile*.

Further reading

Kupers ES, Surawicz CM. Clostridium difficile infection. *Lancet* 2008; **371**: 1486–1488.

FOOD POISONING: *E. COLI* 0157

Enterohaemorrhagic *Escherichia coli* (EHEC)

EHEC (usually serotype O157:H7, and also known as verotoxin-producing *E. coli*, or VTEC) is a well recognised cause of gastroenteritis in man. It is a zoonosis usually associated with cattle, with the organism being found in the intestines of herbivores. There have been a number of major outbreaks (notably in Scotland and Japan) associated with contaminated food. Run off water from where cattle have been grazing is used in irrigation and therefore salads and vegetables are a source of infection, as well as milk and underdone beef, e.g. hamburgers.

EHEC secretes a toxin (Shiga-like toxin 1) which affects vascular endothelial cells in the gut and in the kidney. After an incubation period of 12–48 hours it causes diarrhoea (frequently bloody), associated with abdominal pain and nausea. Some days after the onset of symptoms the patient may develop thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome (HUS). This is more common in children, and may lead to permanent renal damage or death. Treatment is mainly supportive: there is evidence that antibiotic therapy might precipitate HUS by causing increased toxin release.

Case history

A 15-year-old girl is admitted to hospital with bloody diarrhoea; her parents and her three siblings are well. They have apparently all eaten the same food during the last week except on a single occasion when the patient ate a beef-burger cooked at a local party. The mother remembers that it looked rather raw inside. The girl had eaten chicken at least three times during the previous week. She looked slightly dehydrated and had a temperature of 37.8°C. Her abdomen was soft but generally tender, bowel sounds were increased.

What is the differential diagnosis in this patient?

Infectious gastroenteritis with bloody diarrhoea due to:

- *Campylobacter* spp. (chicken the likely source)
- *E. coli* 0157 (beef the likely source)
- *Shigella* spp.
- *Salmonella* spp.
- Onset of inflammatory bowel disease.

Investigations

Should include:

- FBC, including platelets
- U&E (*E. coli* 0157 can cause haemolytic uraemic syndrome)
- Blood culture
- Stools for microscopy, culture and sensitivity

Full clinical details should be put on the form accompanying the stool

Remember

- Most laboratories routinely look for *E. coli* 0157 in people with bloody diarrhoea
- Abdominal X-rays and sigmoidoscopy might also be required if inflammatory bowel disease is considered a likely diagnosis.

What would your initial management be?

The patient should be admitted to MAU and put into excretion–secretion isolation (assuming a probable infective aetiology). Ensure adequate hydration. Oral/IV antibiotics can have a place in treating severe infections due to *Salmonella* spp., *Campylobacter* spp. and *Shigella* spp.; they should not be used in infections caused by *E. coli* 0157. The disease should be notified to the CCDC both by telephone immediately and in writing when the diagnosis has been made. Rapid notification is required if the patient works in the food industry or with the very young, the elderly or the immunosuppressed.

- **Progress.** This patient had *E. coli* 0157 and did not get HUS. She made an uneventful recovery.

Information

Features of haemolytic uraemic syndrome (HUS)

- Intravascular haemolysis with red cell fragmentation (microangiopathic haemolysis)
- Thrombocytopenia
- Acute kidney injury

Mortality is high in the elderly; treatment is by plasma exchange, with some patients requiring haemofiltration dialysis.

TYPHOID

This is the typical form of enteric fever and is caused by *Salmonella typhi*. Enteric fever is an acute systemic illness with fever, headache and abdominal discomfort.

Case history

A 35-year-old Asian male presents with a 1-week history of fever, headache, a dry cough and constipation. He is resident in the UK and has just returned from a 6-week holiday in Bangladesh, where he was visiting relatives. He works as a chef in a local restaurant. While he was away, one of the relatives he was staying with had a high fever and severe diarrhoea.

On examination, the patient had a fever of 39.5°C with a pulse rate of only 85/minute. Examination of the cardiovascular, respiratory and central nervous systems was unremarkable.

The abdomen was slightly tender.

Investigations

- FBC, routine chemistry, CXR and blood cultures taken
- FBC shows a slight leucopenia
- Gram-negative rods are seen in a film of the blood cultures taken after 24-h incubation

What is the most likely diagnosis?

S. typhi (this was later confirmed as being the definitive diagnosis).

How would you manage this patient?

The patient should be nursed in a side room with excretion–secretion precautions used (consult your local infection control manual). The control of infection officer should be alerted, as should your local CCDC, as soon as a definite diagnosis is made. Your CCDC should be alerted immediately by telephone and also via the formal notification book, which should be available on every ward. This is particularly necessary because this patient is a food handler. If the patient subsequently develops diarrhoea, adequate fluids are required to avoid dehydration. Pending antibiotic sensitivity testing, the patient should be commenced on ciprofloxacin 500–750 mg \times 2 daily for 10 days.

NB. Cefuroxime, although frequently used for treating Gram-negative sepsis, is not effective against *S. typhi*, which is an intracellular pathogen.

Remember

Ciprofloxacin is extremely well absorbed and so can be given by the oral route 500 mg 12-hourly as long as the patient is not vomiting. After starting ciprofloxacin the patient started to feel better very quickly but it took 3–6 days for the temperature to settle.

- **Progress.** The patient was discharged after 6 days, feeling well and with no fever. He needed a follow-up appointment to ensure that he does not become a carrier of *S. typhi*. He must remain away from his job as a food handler until he is known to have negative stool cultures for *S. typhi*.

THE RETURNING TRAVELLER

Case history

A 20-year-old student returns from a 6-week backpacking tour of Africa. Two weeks after his return he goes to A&E complaining of fever, headache and malaise of 7 days' duration.

On examination, the patient is thin and febrile with a temperature of 38°C. There are no other abnormal findings.

What further questions do you want to ask this man?

It is essential – as always – to take a full detailed history. Particular note should be taken about exactly where the patient has travelled, what vaccinations he had prior to his trip, whether he took anti-malarial prophylaxis regularly and, if so, what he took. Did he remember being bitten by any insects? Did he have close contact with anyone who was obviously

Table 1.4 Causes of febrile illness in travellers returning from the tropics and world-wide

Developing countries	Specific geographical areas (see text)
Malaria	Histoplasmosis
Schistosomiasis	Brucellosis
Dengue	World-wide
Tick typhus	Influenza
Typhoid	Pneumonia
Tuberculosis	URTI
Dysentery	UTI
Hepatitis A	Traveller's diarrhoea
Amoebiasis	Viral infection Sexually transmitted diseases

WHO advises that fever occurring in a traveller 1 week or more after entering a malaria risk area and up to 3 months after departure is a medical emergency.

URTI, upper respiratory tract infection; UTI, urinary tract infection.

unwell? What sort of food did he eat? Did he have unprotected sex with any strangers while travelling?

Differential diagnosis is shown in Table 1.4.

Remember

Just because someone has been travelling, it does not mean that they can't have a common type of infection such as influenza, a common cold or a sexually transmitted infection. Holidays are notorious for people picking up STIs.

- **Investigations.** Start with simple, cheap and relatively non-invasive investigations whenever possible. Perform other investigations as appropriate, depending on symptoms, signs and results of initial investigations, e.g. imaging (CT scan, ultrasound or MRI) aspiration or needle biopsy.

Investigations

- FBC
- Routine blood chemistry
- Urine analysis
- Blood cultures
- Stool cultures
- CXR
- Thick and thin blood films for malarial parasites: $\times 3$
- Store blood for serology and take a second sample 2 weeks later

- **Diagnosis.** Thick and thin blood films showed that this patient had malaria with a 5% parasitaemia. His malaria was due to *Plasmodium falciparum*. This is a serious infection and requires immediate emergency treatment in an HDU/ITU.

How would you manage the patient?

P. falciparum is resistant to chloroquine. Artesunate 2.5 mg/kg intravenously is very effective and is first line therapy. Alternatively patients with this disease should be commenced on intravenous quinine sulfate 20 mg/kg infused over 4 hours followed by 10 mg/kg infused over 4 hours 8-hourly until the switch to oral therapy (quinine salt 600 mg 8-hourly) can be made. Total dose is for 7 days. Both treatments are followed by a single dose in adults of 3 tablets of pyrimethamine with sulfadoxine (Fansidar). Doxycycline 200 mg once daily for 7 days can be used as an alternative to pyrimethamine and sulfadoxine. Intravenous quinine might potentiate hypoglycaemia and patients on it should have their blood sugar monitored regularly. Ideally, they should also be on cardiac monitors.

- **Progress.** This young man made a full recovery. He admitted that he had not taken his malaria prophylaxis regularly.

Further reading

WHO new guidelines. www.who.int/topics/malaria/en/

SHINGLES

Varicella zoster virus causes a primary infection – chickenpox, usually in children.

The virus remains latent in dorsal root and cranial nerve ganglia and reactivation results in shingles.

Case history

A 75-year-old man presents to his GP with severe right-sided chest pain for the previous 2 days. In the past 24 hours he has noted a rash on the right side of his chest, in the distribution of T5–T6.

What do you think the likely diagnosis is?

Shingles.

What question would you like to ask the patient?

Have you had chickenpox?

Remember

Not everyone who has antibodies to *Varicella zoster* virus remembers having the primary disease.

The FDA in the USA recommends that all people over the age of 65 years should have prophylactic varicella inoculation.

What investigations might you perform?

The disease is usually diagnosed clinically. It can be confirmed by examination of the vesicular fluid under an electron microscope to look for herpes virus. Serology can also be performed.

How would you manage the patient?

This patient requires admission to hospital (see below). He should be nursed in a side room and only by nurses who are known to have antibodies against varicella zoster virus. (If he had remained at home, he must avoid contact with people who have no history of having had chickenpox.

As the patient has had the rash for less than 3 days he should be commenced on aciclovir. Alternative anti-viral agents active against varicella zoster virus include famciclovir or valaciclovir. The usual adult dose of aciclovir for treatment of shingles is 800 mg five times per day by mouth or 5 mg/kg three times per day if given intravenously.

Remember

Modification of the dose of aciclovir might be required if the patient has renal impairment

- Patients should be prevailed upon not to scratch their lesions as this can predispose to secondary infection
- Calamine lotion can help. Patients are likely to require analgesia.

- **Progress.** The patient was admitted to hospital because he lives on his own. He was started on oral aciclovir 200 mg \times 5 daily. 24 h later he developed a high fever. A nurse noticed that one of the lesions had an inflamed area around it.

What do you think has happened? How would you manage the patient?

Secondary infection of the shingles lesions has occurred. The most likely pathogens to cause this are *Streptococcus pyogenes* or *S. aureus*. Swabs should be taken and sent to Microbiology for microscopy, culture and sensitivity and blood cultures should also be taken. The patient was commenced on IV benzylpenicillin (active against *Strep. pyogenes*) and IV flucloxacillin (active against *S. aureus*) and switched to oral therapy after 3 days. His infected area settled but on discharge after 6 days he still had a painful area of shingles on his chest with some new lesions. His aciclovir was therefore continued for 10 days.

He was also given amitriptyline 10 mg at night for pain. He remained unwell for 3 weeks but after 2 months his pain had settled and he made a full recovery.

Information

Ophthalmic herpes is infection of the 1st division of the Vth nerve and can lead to corneal scarring and secondary panophthalmitis. *Ramsay Hunt syndrome* is due to herpes infection of the geniculate ganglia. It causes a facial palsy with vesicles on the pinna of the ear. *Post-herpetic neuralgia* is a burning continuous pain in the area of the previous eruption. It is common in the elderly and accompanied by depression. It is difficult to treat.

Further reading

Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *New England Journal of Medicine* 2002; **347** (5): 340–346.

EPSTEIN-BARR VIRUS

This virus causes an acute febrile illness, usually in teenagers or young adults and is known as infective mononucleosis (glandular fever). It is transmitted by saliva or aerosol.

Case history

A 19-year-old college student presents to his doctor with a 1-week history of severe sore throat, fever and extreme fatigue.

On examination, the patient is found to have a fever of 38.8°C, and cervical, axillary and inguinal lymphadenopathy.

The tonsils appear enlarged and his pharynx erythematous with palatal petechiae present.

The spleen is just palpable.

What is the likely diagnosis in this patient?

The most likely diagnosis in a person of this age with a short history of fever, malaise, general lymphadenopathy and severe sore throat is infectious mononucleosis (glandular fever).

Streptococcal sore throats can mimic infectious mononucleosis clinically, although hepatosplenomegaly and inguinal and axillary lymphadenopathy will be absent.

Cytomegalovirus infections and toxoplasmosis also present in a similar fashion, although the sore throat is usually less severe. Viral hepatitis can also sometimes present with fever, lymphadenopathy, malaise and an atypical lymphocytosis. HIV seroconversion can also present as a glandular-fever-like illness. Lymphomas and leukaemia occasionally present in this way.

How would you confirm the diagnosis?

A full blood count should be performed. In over two-thirds of patients this will show a mononuclear lymphocytosis with atypical lymphocytes

present. A mild neutropenia is frequently present and platelet counts are commonly slightly decreased. Serum aminotransferases are usually raised.

Heterophile antibodies that agglutinate sheep red blood cells (the Paul–Bunnell test) usually become positive during the second week of infection.

The Monospot test (a rapid screening test) will be positive in glandular fever in 85% of cases. In addition, EBV-specific antibodies can be looked for in Paul–Bunnell-negative ‘glandular fever’ or in atypical cases, but these are generally not performed. Ask your local virology laboratory for further details, if required.

Treatment

Generally supportive. Contact sports should be avoided while splenomegaly is present. Aspirin helps relieve the sore throat and reduce fever. Occasionally, the tonsils can be so swollen that airway obstruction seems imminent: in these cases a short course of steroids is helpful, usually commencing with approximately 60 mg prednisolone/day in individual cases and stopping within 1–2 weeks. Corticosteroids are also indicated in cases with marked thrombocytopenia, haemolysis or CNS involvement.

Remember

About 90% of patients with infectious mononucleosis who are given ampicillin and amoxicillin will develop a rash.

If the diagnosis is unclear, if it is suspected that the patient might have a sore throat due to *S. pyogenes* or if a secondary streptococcal infection is suspected, the patient should be commenced on intravenous benzylpenicillin (if in hospital) pending culture and serology results. If the patient is not admitted, high-dose oral penicillin is an alternative.

- **Prognosis.** This student’s sore throat and fever settled after 5–6 days but he still felt unwell for a further 3 weeks.

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HIV/AIDS

Case history

A 35-year-old European man is newly diagnosed HIV positive. He was tested because he had been feeling generally unwell over a 6-month period and had lost weight. He presents with a persistent cough, which has developed and worsened over the preceding 2 weeks.

On examination he has a temperature of 39°C, his pulse is 100/min and he has a respiratory rate of 20/minute.

There are signs of oral candidiasis. He is on no regular medication. You are the medical SHO on acute take.

What are the likely diagnoses and the immediate management?

Pneumocystis jiroveci pneumonia commonly has an insidious onset, often with worsening shortness of breath and deteriorating exercise tolerance; the cough is usually non-productive.

- Examination of the chest can yield few signs other than tachypnoea and tachycardia. Fine inspiratory crackles might be heard.
- The CXR is often normal or shows little, although bilateral perihilar interstitial shadowing with a bat-wing appearance is the characteristic abnormality.
- High-resolution CT of the lungs shows a characteristic ground glass appearance even when there is little to see on the plain CXR.
- Oxygen saturation characteristically falls on exercise. Arterial blood gas analysis might show hypoxia with a normal carbon dioxide and pH.
- The diagnosis is made on broncho-alveolar lavage.

The introduction of highly active anti-retroviral therapy (HAART) in HIV-infected people has led to a significant decline in pneumocystis and the infection is now most commonly seen in those not previously recognised as HIV infected. Pneumocystis infection occurs most frequently in the context of significant immunosuppression, when the CD4 count is < 200 cells/mm³. There may be clinical markers of poor immune function, such as candidiasis, as in this patient.

Primary prophylaxis (cotrimoxazole is first line) is recommended in those who are aware of their HIV status if their CD4 count falls into this range. This intervention alone has reduced the incidence of pneumocystis infection in HIV-infected populations. Pneumocystis pneumonia is an AIDS-defining diagnosis.

How would you treat this patient?

IV cotrimoxazole (trimethoprim 15 mg/kg/day + sulfamethoxazole 75 mg/kg/day) is the preferred first-line treatment, although a significant proportion of patients will develop allergy. IV pentamidine or dapsone plus pyramethamine are also used.

Treatment is given for 3 weeks. Systemic corticosteroids (IV methylprednisolone 40 mg × 4 daily for 5 days) are added in severe cases (PO_2 less than 8 kPa). Patients with pneumocystis infection can develop respiratory failure and require ventilatory support. Pneumothorax is a further complication of pneumocystis.

The organism is not cleared by treatment and secondary prophylaxis (usually cotrimoxazole) is recommended. This can be withdrawn later if the patient starts HAART and the CD4 count remains consistently > 200 cells/mm³.

In a patient not already on HAART, initiation of therapy should be discussed with a specialist physician.

What other chest conditions are associated with HIV?

Mycobacteria tuberculosis (MTB)

An organism of high pathogenicity, MTB can develop relatively early in the course of HIV infection. It is particularly common in those who have lived in areas of the world with a high incidence of MTB, e.g. sub-Saharan Africa. Pulmonary infection presents with a cough (usually productive) and chest pain but, in the context of HIV infection, presentation is often insidious and non-specific, with fever, sweats, malaise and weight loss. History of contact with MTB should always be sought, along with details of any previous anti-tuberculous therapy, because in such patients there is a risk of multidrug-resistant tuberculosis (MDRTB). There might be generalised lymph node enlargement or hepatomegaly in addition to signs in the chest. In some cases pulmonary infection is coupled with CNS involvement – either TB meningitis or tuberculoma. The chest radiological changes are few and are frequently atypical, with lower zone changes without cavitation. Other radiological findings include hilar lymphadenopathy, pleural effusion or lobar consolidation.

In patients with HIV, the usual immunological reactions to MTB might be blunted or absent, making diagnosis more difficult. Mantoux tests are rarely helpful because immunosuppressed patients do not produce a normal delayed hypersensitivity reaction. Granuloma formation can be compromised, leading to atypical histological changes. Sputum smears may be negative in up to 50% of those with culture-proven TB. Diagnosis relies heavily on clinical suspicion backed by positive cultures from, e.g. sputum, broncho-alveolar lavage, blood, bone marrow, lymph nodes, as appropriate.

Treatment of TB in HIV co-infected patients presents specific challenges and requires input from a specialist physician. Treatment is similar to that for HIV-negative patients, although intermittent and short-course regimens are not advised.

Therapy should be initiated with four drugs – isoniazid, rifampicin, pyrazinamide and ethambutol – for 2 months. Once sensitivities are confirmed, pyrazinamide and ethambutol can be withdrawn and the other two drugs continued for 4 months, although this might be extended in some circumstances. The drug-drug interactions between anti-retroviral

and anti-tuberculous medications are complex and are a consequence of enzyme induction or inhibition. There are interactions between rifampicin derivatives and the protease inhibitor class of anti-retroviral agents, leading to an increase in rifampicin toxicity and reduced protease efficacy. The non-nucleoside reverse transcriptase class also interacts variably with rifampicin, requiring dose alterations. Additionally, there are overlapping toxicities between HAART regimens and anti-tuberculous drugs, in particular hepatotoxicity, peripheral neuropathy and gastrointestinal side effects.

Remember

Any patient in whom the suspicion of TB is great enough to start anti-tuberculous therapy MUST be notified to the local consultant in communicable disease control (CCDC).

Paradoxical inflammatory reactions (e.g. immune reconstitution inflammatory syndrome, IRIS), which include exacerbation of symptoms, new or worsening clinical signs and deteriorating radiological appearances, have been associated with improvement of immune function. IRIS is most commonly seen in the first few weeks after initiation of HAART in patients recovering from MTB, and can last several weeks or months. The syndrome does not reflect inadequate TB therapy and is not confined to any particular combination of anti-retroviral agents. It is important to exclude new pathology in this situation.

Bacterial chest infection

Several respiratory infections are more common in patients with HIV infection, in particular *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. The onset is usually rapid, with a productive cough. Signs of consolidation occur and radiological changes of consolidation or infiltration might be present. Diagnosis is based on sputum and blood cultures and management is with appropriate broad-spectrum antibiotics (e.g. cefotaxime).

Other infective conditions

Cytomegalovirus, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Histoplasma capsulatum* and *Nocardia asteroides* can all cause fever, cough and dyspnoea in association with advanced HIV infection. The clinical signs and radiological findings are usually non-diagnostic. The diagnosis depends on broncho-alveolar lavage.

Malignancy

The incidence of **Kaposi's sarcoma** (KS) has declined significantly since the widespread introduction of HAART. It is a vascular tumour that is associated with human herpes virus type 8 (HHV8). Although most commonly found on the skin, KS can infiltrate the lungs to cause cough and shortness of breath. On examination, other KS lesions are usually found on the skin or in the mouth, but in rare cases the lungs alone may be involved.

Radiological changes are of diffuse lung infiltration often with a nodular appearance. Pleural effusion might be present. Lesions are visualised on

bronchoscopy. Treatment is with systemic chemotherapy. Anti-retroviral therapy should be initiated if the patient is not already on treatment.

Non-Hodgkin's lymphoma can also cause lung infiltration. Patients additionally present with systemic 'B' symptoms. On examination lymphadenopathy and splenomegaly might be found. Hilar lymphadenopathy seen on the CXR and CT scan indicate widespread lymph node enlargement in the chest and abdominal cavities. The diagnosis is made on the histological appearance of lymph node biopsy. Such lymphomas are often aggressive. Treatment is with chemotherapy (see Kumar and Clark, *Clinical Medicine* 6th edn, p. 510).

How would you manage an HIV-positive patient with chest problems?

The differential diagnosis in an HIV-infected patient presenting with respiratory symptoms is wide. There is considerable advantage in establishing a specific diagnosis rather than treating symptoms empirically. Factors that impact on diagnosis and management include the clinical presentation, the level of immunosuppression of the individual, lifetime exposure to infective agents and current medication.

Remember

In HIV-infected patients:

- Common conditions can have unusual presentations
- Uncommon conditions occur more frequently
- Many different conditions can present in similar ways – clinically and radiologically
- Those standard investigations that depend on an intact immune system will not be useful
- A tissue or culture diagnosis is frequently required. Pathology in HIV-infected patients is related to:
 - Their degree of immunosuppression
 - The virulence of the organism
 - The microbiological repertoire to which an individual has been exposed
 - The multiple pathology that is frequently encountered
 - The medication that the patient is taking.

Assessment

- Full history and examination: including details of travel, previous infections, previous or existing HIV-related pathology, current surrogate marker data (if known), current therapy including anti-retroviral drugs and anti-microbial prophylaxis.
- Assess the degree of immunosuppression by looking for clinical signs such as oral candidiasis, hairy oral leukoplakia, and seborrhoeic dermatitis. Look for pathology in all systems, including examination of the mouth and fundi.
- Chest X-ray, exercise oximetry, blood gases, blood cultures, sputum examination for acid-fast bacilli (AFB), and microscopy, culture and sensitivity. Full blood count, liver and renal function.

Treatment

If the patient is clinically immunosuppressed, has a previous AIDS-defining illness or is known to have a CD4 count $< 200/\text{mm}^3$ and has chest X-ray abnormalities or desaturates on exercise, or has a hypoxic blood gas picture suggestive of pneumocystis infection, institute therapy pending bronchoscopy. Organisms will still be found several days into treatment.

Remember

- Drug allergies
- Bone marrow suppression with high-dose cotrimoxazole
- Hypotension/hypoglycaemia with IV pentamidine
- CD4 counts and HIV viral load measurements are altered in the face of any acute infection and might not accurately reflect the underlying situation.

If the patient has a history of TB or of exposure to TB, or has clinical and radiological findings consistent with TB, isolate the patient and investigate. Do not initiate empirical anti-tuberculous therapy without an expert opinion, as this will have long-lasting and far-reaching consequences for the patient and for future management.

If the patient has sputum smear positive for AFB or has culture-proven TB, isolate and start anti-tuberculous therapy with four drugs. Notify and seek expert opinion.

If the patient has clinical or radiological signs of bacterial infection, institute therapy with broad-spectrum antibiotics, e.g. amoxicillin or azithromycin.

Remember

- If the patient does not respond as detailed:
- Reconsider the diagnosis
 - Suspect multiple pathology.

Further reading

Skolnik PR. HIV therapy. *New England Journal of Medicine* 2003; **349** (24): 2351–2352.

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FEEDING THE PATIENT

Case history

A surgical colleague phones you to ask about parenteral nutrition for a 70-year-old man who had an oesophago-gastrectomy 5 days previously. Postoperative care had been straightforward and no prior provision for parenteral nutrition had been made. It now seems likely that he has an anastomotic leak.

What should you advise?

Parenteral nutrition is never an emergency therapy. It can always wait until expert advice is available next day. You say that you will bring your consultant along the following morning.

Remember

- It is better to predict (if possible) whether some form of supplementary nutrition is likely to be required **before** an event
- Over 10% of patients in hospital are said to be malnourished.

How do you assess the nutritional state?

This can be done simply by looking at the patient! Does he look malnourished? Other parameters that can help are:

- Weight loss > 10%
- Serum albumin < 35 g/L
- Serum transferrin < 1.5 g/L
- Body mass index (BMI) = (kg) ÷ height (m²); the normal range is 18.5 to 24.9.

An evaluation of the nutritional status can be done using the MUST criteria (Fig 3.1).

Nutrition will be necessary for

- All severely malnourished patients on admission to hospital
- Moderately malnourished patients who are not expected to eat for 3–5 days because of their illness
- Normally nourished patients not expected to eat for 7–10 days.

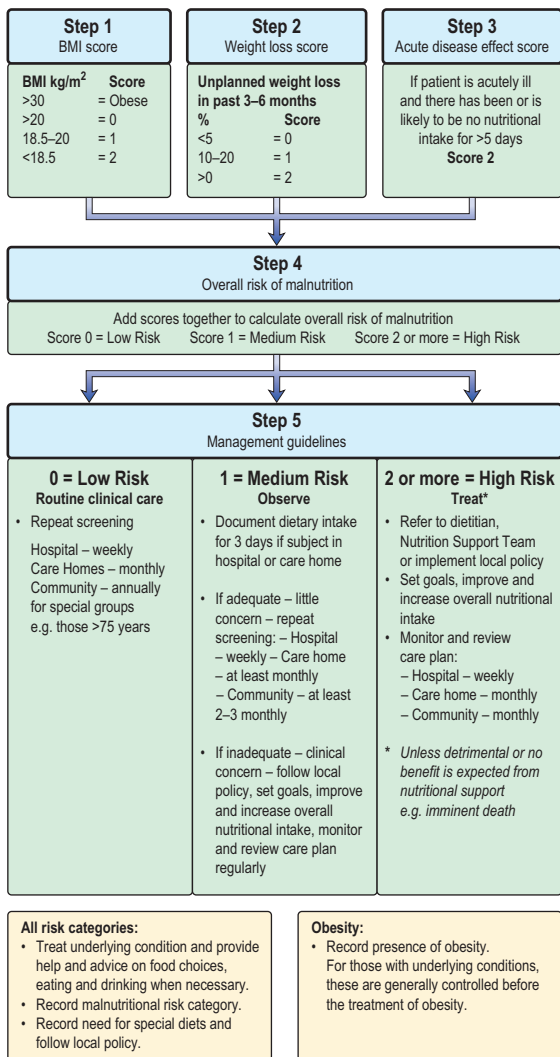


Figure 3.1 'Malnutrition Universal Screening Tool' ('MUST'). Reproduced with permission from the British Association for Parenteral and Enteral Nutrition (BAPEN): www.bapen.org.uk.

Always feed enterally rather than parentally if possible

Information

Standard enteric diet providing 8.4 MJ per day (2000 kcal)

Energy:

- Carbohydrate as glucose polymers (49–53% of total energy)
- Fat as triglycerides (30–35% of total energy)

Nitrogen

Whole protein (6–7 g of nitrogen/L)

Other

Additional electrolytes, vitamins and trace elements.

This provides:

ratio of energy:nitrogen kJ : g = 620:1 (ratio of energy kcal:
nitrogen : g = 150 : 1).

Osmolality = 285–300 mOsmol/kg.

See current *National Formularies* for ready-made formulations.

Methods of enterally feeding

- By mouth
- By fine-bore nasogastric tube (check position with pH paper and if in doubt, X-ray. Feeding tubes are usually placed endoscopically)
- Percutaneous endoscopic gastrostomy (PEG; refer to gastroenterologist for insertion) for prolonged period, i.e. > 30 days.

Methods of parenteral nutrition

Peripheral nutrition is the initial preferred option. Peripheral cannulas are inserted into the mid arm vein. Each catheter will last 5 days and the procedure has fewer complications than a central venous catheter.

Central nutrition. A cannula is inserted via an intra-clavicular approach into the subclavian vein in theatre. Infusions include nitrogen for protein synthesis, calories, electrolytes, vitamins and trace elements. Complications include sepsis, thrombosis, pneumothorax and embolism.

Most hospitals have nutrition teams to advise on the nutritional regimens that are required.

Remember

Remember to monitor carefully with:

- daily plasma electrolytes
- daily glucose
- weekly assessments of nutritional status.

- **Progress.** This patient was not suitable for enteral nutrition because of his gastrointestinal surgery; thus parenteral nutrition is appropriate.

He was started with peripheral nutrition via a mid arm cannula. However, after 5 days it was felt he required longer-term nutrition and a central

catheter was inserted. The leak settled on conservative management and he was able to return home on soft foods 4 weeks later.

Further reading

The Journal of Parenteral and Enteral Nutrition (JPEN). www.nutritioncare.org/wcontent.aspx?id=172

National Institute for Health and Clinical Excellence. Nutrition support in adults. Clinical Guideline 2006; 32: www.nice.org.uk

Singer P, Berger MM, Van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. *Clin Nutr* 2009; **28**: 387–400.

VOMITING

Vomiting centres are located on the lateral reticular formation of the medulla and are stimulated by chemoreceptors trigger zones on the floor of the 4th ventricle and also by vagal afferents from the GI tract.

Causes of vomiting are shown in [Table 4.1](#).

Case history

A 70-year-old man was admitted with a 2-week history of repeated vomiting. He had lost more than 6 kg in weight. He had recently developed colicky abdominal pain and constipation without passage of wind.

On examination, his abdomen was distended and he was tender in the epigastrium.

You call for surgical advice. The surgeon, in addition to your findings, notes that there are increased bowel sounds. The patient's hernial orifices and rectal examination show no abnormality.

Remember

Non-gastrointestinal causes are possible: a full examination is therefore necessary. *Note:* look at the fundi for papilloedema.

Table 4.1 Causes of vomiting

Any gastrointestinal disease

Infections

Viruses (influenza, norovirus)
Bacterial (pertussis, urinary infection)

Central nervous system disease

Raised intracranial pressure
Vestibular disturbance

Migraine

Metabolic

Uraemia
Hypercalcaemia

Diabetic ketoacidosis

Drugs

Antibiotics
Chemotherapy
Digoxin
Immunotherapy

Incretins
Levodopa

Opiates

Reflex

Myocardial infarction
Biliary colic

Psychogenic

Pregnancy

Alcohol excess

Investigations

- Haematological:
 - FBC, ESR, CRP
- Radiological:
 - Abdominal X-ray
 - Chest X-ray
- Biochemical:
 - Electrolytes
 - Urea/creatinine/eGFR
 - LFTs
 - Calcium
 - Amylase

- **Chest X-ray (CXR).** Normal. Look for evidence of air under the diaphragm (perforation), signs of pneumonia, hilar mass (tumour).
- **Abdominal X-ray (AXR).** Normal. With a history of this length, a normal X-ray would suggest that large or small bowel obstruction is unlikely. High obstruction in the gastrointestinal (GI) tract, i.e. in the oesophagus or stomach, is possible. Investigate for non-GI causes (metabolic, neurological – exclude brainstem lesion), occasionally severe depression.
 - **Abnormal.** Might show evidence of small or large bowel obstruction or gastric distension.

In this patient, the AXR showed small bowel obstruction (Fig. 4.1). The differential diagnosis is shown in the Information box.

Information

Small intestinal obstruction: differential diagnosis:

- Adhesions (80% in adults)
- Hernia
- Crohn's disease
- Intussusception
- Obstruction due to extrinsic involvement by cancer

Management

The ultimate goal is to relieve obstruction. In the interim:

- Infuse glucose/saline to maintain electrolyte balance (with additional K^+ 20 mmol per litre).
- Insert nasogastric tube (on continuous drainage).
- Contact surgeons, await instruction as to further investigations (such as CT scan to localise obstructive lesion).
 - **Progress.** At operation, a carcinoma of the ascending colon was found and resected.

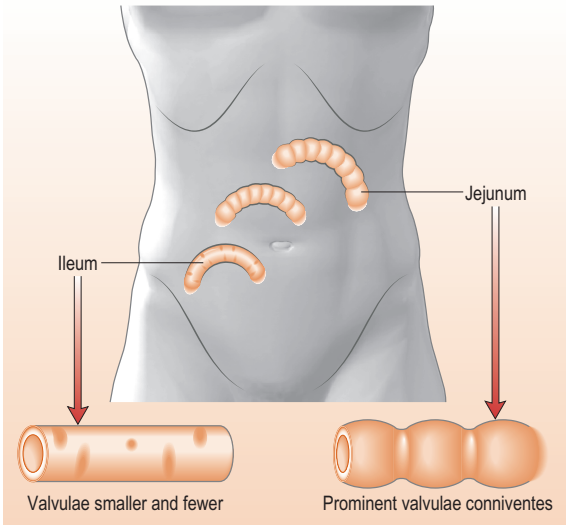


Figure 4.1 Small bowel obstruction, showing dilated loops of small bowel.

HICCUPS

Hiccups are due to involuntary diaphragmatic contractions with closure of the glottis. They are very common and usually not sinister, even if persistent.

Case history

You are called by the surgical SHO because he is concerned that a 70-year-old man has had continuous hiccups for 48 h, a fever, malaise and right hypochondrial pain. Ten days ago he had been admitted with intestinal obstruction (see case above) and a laparotomy for a carcinoma of the ascending colon had been performed. This is a classic situation for a **subphrenic abscess** occurring post-surgery in an elderly person.

How would you investigate?

Check Hb, WBC and liver biochemistry. An urgent ultrasound was performed and confirmed the diagnosis of a subphrenic abscess. Blood cultures were taken as he was febrile.

Treatment and prognosis of the abscess

He had drainage under ultrasound control and antibiotics were started. The bacteria causing abscesses are usually *Bacteroides* spp. and/or *E. coli*

and he was therefore treated with a cephalosporin and metronidazole. His hiccups were controlled with chlorpromazine 50 mg or diazepam 5 mg as necessary.

Other causes of hiccups

- Metabolic, e.g. uraemia
- Neurological, e.g. brainstem tumour
- Other abdominal pathology
- No pathological cause.

WEIGHT LOSS

Weight loss is often a perceived symptom by patients but does need to be verified. It is a general symptom, which can reflect disease in any part of the body.

Always make sure that the patient has a sufficient calorie intake for his/her requirements, bearing in mind the amount of exercise taken. In a young female, think of anorexia nervosa.

Reduced calorie intake can be due to intentional dieting but can also be a symptom of generalised disease due to anorexia.

Case history

A 40-year-old man has been admitted with a fever, tremor and 10 kg weight loss. He has previously been counselled for alcohol misuse.

What should you do?

You need to consider a number of diagnoses and this might be helped by additional history and examination:

- Hyperthyroidism: check for symptoms and signs of hyperthyroidism (see p. 434).
- Alcoholic liver disease (see p. 70).
- Malnutrition: check by asking the patient's family. Perhaps there is a psychiatric history?
- Underlying cancer, particularly lung, bowel and pancreas.
- Biochemical investigations: should help determine underlying metabolic or renal disease.
- Malabsorption: often causes anorexia, which contributes to weight loss.

This patient had no major signs of chronic liver disease but did admit to recurrent episodes of upper abdominal pain radiating through to his back. These tended to occur on Monday, following his weekend binges. This suggests **pancreatic disease** resulting from his heavy alcohol intake.

What initial investigations are appropriate?

- FBC, LFTs, calcium, blood alcohol
- Plain X-ray of the abdomen for pancreatic calcification
- Abdominal ultrasound to assess the pancreas for cysts and potential masses.

This patient was admitted in a malnourished, hyperdynamic state due to **acute alcohol withdrawal** (see p. 72). Treat this initially and further investigate the pancreas later.

Further investigations

- CT scan of the pancreas:
- MRCP: this is non-invasive and of value in assessment of the pancreas and biliary tree
- ERCP to delineate the biliary and pancreatic ducts (if MRCP is unavailable)
- Endoscopic ultrasound: can help define pancreatic cysts and masses

- **Progress.** This man was treated initially with benzodiazepine and IV thiamine (p. 527) and made a good recovery from his acute withdrawal state. Further investigations showed chronic pancreatitis; he was referred to the Gastroenterology Clinic.

DYSPHAGIA

Dysphagia is difficulty in swallowing. It is an immediate, obstructive sensation during the passage of liquid or solid through the pharynx or oesophagus.

Case history

A 55-year-old patient has been referred urgently because of acute dysphagia. She gave a history of reflux for years and increasing dysphagia for 6 months. She had been eating an orange, which became lodged in her gullet and all efforts to dislodge it were unsuccessful. The underlying diagnosis is likely to be **food bolus obstruction** on an already present oesophageal stricture.

What should you do?

Refer for an urgent endoscopy. The endoscopy findings were of a stricture in the mid-oesophagus with no obvious malignant lesion. Biopsies were taken and the stricture dilated.

Remember

Submucosal cancer can look like a benign lesion.

Unfortunately, this woman developed severe chest pain immediately after the dilatation and surgical emphysema could be felt in her neck. Clinically, an oesophageal tear is suspected.

A CXR with a water soluble contrast agent orally, confirms an oesophageal rupture.

- **Diagnosis.** The underlying cause is more likely to be **oesophageal cancer** because careful dilatation of benign lesions rarely causes a tear.

Initial management

- Nil by mouth
- IV line for fluids
- Antibiotic prophylaxis
- Surgical referral.

Small tears in a peptic stricture can resolve in a few days on conservative management. Large tears generally need surgery in a dedicated thoracic unit. Endoscopic stenting is used initially for tears in malignant lesions but again surgery may be required.

Biopsies later confirmed a **squamous carcinoma**.

Management will include assessment for surgery with:

- Blood count, liver biochemistry
- CXR
- ECG
- Respiratory function tests
- Abdominal US, CT scan to assess operability
- Endoscopic ultrasound is an accurate way of staging lesion and any local lymph nodes
- PET scan to look for distant metastases.

Discussion should take place at an MDT to decide on the patient's treatment.

As investigations showed no distant metastases, surgery with neoadjuvant (preoperative) and adjuvant (postoperative) chemoradiation treatment was given.

CONSTIPATION

This is the infrequent passage of stools, < 3 per week + straining and the passage of hard stools.

Case history

Your house officer asks you what she should prescribe for an elderly man who hasn't opened his bowels for 5 days. The patient, who was previously well and active, had been admitted a week ago with a chest infection. Rectal examination revealed a loaded colon with no local lesion.

Should this patient be investigated?

Not initially because it seems likely that constipation is due to immobility. A barium enema may be necessary if there is no improvement.

Treatment

- Initially, the patient will require a laxative to 'get things moving'. Glycerol suppositories are useful. Oral magnesium sulphate, an osmotic purgative, is effective and cheaper than the more usually prescribed osmotic laxative lactulose.
- Do not use stimulant laxatives.
- Stop 'constipating' drugs if possible.
- Faecal impaction might require digital extraction followed by small-volume phosphate enemas.
- Advise the patient regarding high-fibre diets and fluid intake.

Information

Causes of constipation:

- Simple/idiopathic
- Intestinal obstruction
- Colonic disease, e.g. carcinoma
- Painful anal conditions
- Drugs, e.g. codeine, iron, verapamil, tricyclic anti-depressants, opiates
- Hypothyroidism, hypercalcaemia
- Depression
- Immobility

DIARRHOEA

Increased frequency of defecation can, even in a previously fit patient, produce dehydration and *severe* electrolyte depletion. Diarrhoea can also be a recurrent problem in patients with established gastrointestinal disease.

What should you do in a case of diarrhoea presenting in A&E?

In the history, ascertain whether the patient has eaten suspect food or travelled overseas. Check for drug history, e.g. antibiotics. Ask about accompanying symptoms, e.g. abdominal pain, weight loss. It is essential to:

- Establish history of onset.
- Determine frequency, consistency, content of stool, presence of blood.
- Determine the state of hydration and electrolyte balance.
- Send stool for culture, parasites (ova or cysts) and *C. difficile* toxin (if the patient has previously been hospitalised or been on antibiotics).
- Perform a rectal examination; sigmoidoscopy (if bloody diarrhoea) should be done by the gastroenterology team.
- Do blood cultures in severe cases with a temperature.
- Do a plain abdominal X-ray.

Information

Likely pathogens causing diarrhoea**Bacteria (50%):**

- *E. coli*
- *Campylobacter* spp.
- *Salmonella* spp.
- *Shigella* spp.

Viruses (1% but seldom produce severe diarrhoea in adults):

- Rotavirus
- Noravirus

Protozoa:

- *Giardia*
- *Entamoeba histolytica*
- *Cryptosporidium*

Helminths (e.g. *Strongyloides*):

Some cases have no pathogens or multiple pathogens found (this occurs in 20–50% of cases).

Management

This will depend on the case scenario (see below) but most diarrhoeal illnesses are self-limiting and short lived; 1–10% might persist for a month. Identification of the pathogen will determine specific therapy (see Chapter 1).

Case history (1)

A 24-year-old returned from travelling for 3 months, during which he passed through several countries. He was fairly well on his return but after 3 days he developed severe diarrhoea which has now been present for 2 weeks.

On admission to MAU he is dehydrated and has lost over 5 kg in weight.

What immediate action would you take?

- FBC, U&Es, LFTs.
- Send stools for ova, cysts and culture.
- Rehydration with oral glucose/electrolyte solutions initially. IV fluids are usually not necessary.
- Vomiting might need to be treated with an anti-emetic (metoclopramide 10 mg × 3/day).

Diagnosis

This is not acute diarrhoea due to a viral/bacterial cause as the patient did not have diarrhoea when he returned to the UK. Viral/bacterial diarrhoea usually starts in the country where the infection occurred and generally clears up within 7 days. Possible causes are shown in the Information box.

Information

Causes of non-acute diarrhoea in a returning traveller:

- Giardiasis
- Cryptosporidiosis
- Amoebiasis
- Tropical sprue (SE Asia, Caribbean)
- Schistosomiasis
- Strongyloidiasis

Stool samples showed no abnormal findings.

- **Progress.** Giardiasis is very likely in this patient and treatment with metronidazole 2 g a day for 3 successive days was given, with dramatic improvement.

Case history (2)

A 30-year-old, white, Caucasian, female patient presented with a 2-week history of passing six to ten motions a day. The stools were loose and contained blood. She felt tired and had lost about 5 kg in weight.

On admission to MAU she was not dehydrated but had a fever and was very lethargic.

What is the differential diagnosis?

- Infective diarrhoea. Send specimens for microbiological testing.
- First presentation of inflammatory bowel disease (most likely in this woman).

Inflammatory bowel disease (IBD)

In any case of persistent diarrhoea presenting in A&E in developed countries, IBD is a possible cause. A previous history of intermittent diarrhoea or recurrent abdominal pain is often present. In developing countries, infective causes are more likely and must be excluded.

What should you do?**General**

- Take blood for FBC, ESR, CRP, urea and electrolytes, liver biochemistry.
- Check plain abdominal X-ray for presence of stool, mucosal oedema, bowel dilatation or perforation.
- Sigmoidoscopy: the presence of an inflamed, friable mucosa with loss of vascular pattern or a patchy inflammation indicates inflammatory bowel disease. Take a rectal biopsy.
- Stool cultures (NB: Infective gastroenteritis must always be ruled out). *C. difficile* toxin assay – 4 stool specimens (90% sensitivity).

In this patient you have ruled out infective gastroenteritis as three stool cultures were negative. Taking into account the history and the

Table 4.2 Findings in severe attack of ulcerative colitis

Haemoglobin	↓	< 100g/L
Albumin	↓	< 30g/L
Fever	↑	> 37.5°C
Stool frequency	↑	> 6/day
Erythrocyte sedimentation rate	↑	> 30mm per hour
Pulse rate	↑	> 90bpm
Platelets	↑	
White blood cells	↑	

sigmoidoscopic finding, you presume this must be inflammatory bowel disease. Her Hb was 100 g/L and CRP 84 mg/L.

Acute colitis is associated with diarrhoea, abdominal pain, fever and systemic disturbance. There is blood in the stools in ulcerative colitis but Crohn's disease patients only have bloody diarrhoea with Crohn's colitis. To assess severity, check the factors shown in Table 4.2.

Always look for the presence of:

- Toxic dilatation: colon > 5 cm diameter and mucosal islands on plain abdominal X-ray (Fig. 4.2).
- Perforation (on abdominal X-ray).

How would you manage this acute situation?

- IV fluids with glucose/saline.
- IV therapy with steroids (IV hydrocortisone 100 mg × 4/day) followed by oral therapy (enteric coated prednisolone 40 mg per day) if patient improves.
- IV antibiotics (metronidazole/cephalosporin).
- Further management: refer to gastroenterologists; consult GI surgeons.

Remember

In acute severe ulcerative colitis, at 3 days post treatment and CRP > 45 mg/L or stool frequency > 8/day gives an 85% chance of needing a colectomy.

Progress and management

There was no response to treatment at 3 days (see Information box). She was started on infliximab 5 mg/kg as 'rescue therapy' to avoid immediate colectomy. Ciclosporin 2 mg/kg/day is an alternative.

This patient responded to infliximab and is being followed closely in the Colitis Clinic, continuing on infliximab therapy on a protocol, lasting up to 46 weeks.

Has this patient got Crohn's disease or ulcerative colitis?

Both can produce an acute colitis. The differentiation is by colonoscopy and histological appearance (see Table 4.3).

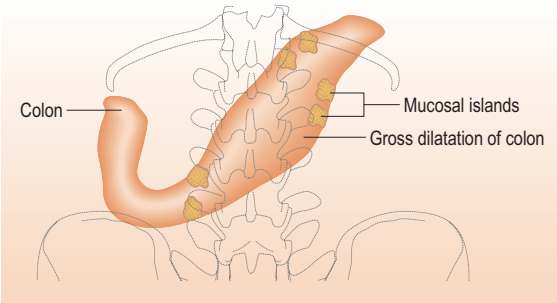
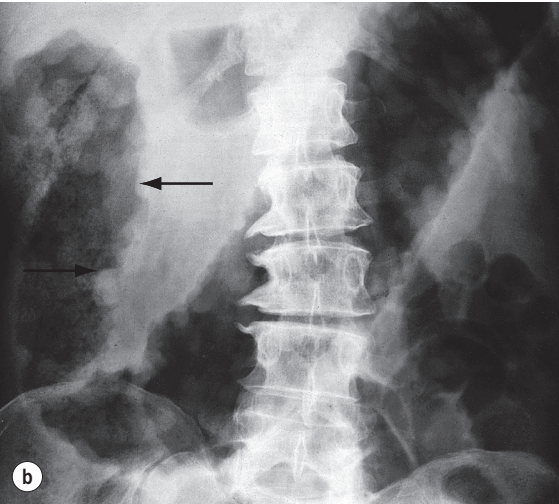
**a**

Figure 4.2 (a) Toxic dilatation of the colon; (b) plain abdominal X-ray showing toxic dilatation in ulcerative colitis.

Table 4.3 Differentiating between Crohn's disease and ulcerative colitis

Histological findings	Crohn's disease	Ulcerative colitis
Inflammation	Deep (transmural), patchy	Superficial (mucosal) continuous
Granulomas	+ +	Rare
Goblet cells	Present	Depleted
Crypt abscesses	+	+ +

Table 4.4 Extra-gastrointestinal manifestations of inflammatory bowel disease

Eyes	Uveitis
	Episcleritis, conjunctivitis
Joints	Type I (pauci-articular) arthropathy
	Type II (polyarticular) arthropathy
	Arthralgia
	Ankylosing spondylitis
	Inflammatory back pain
Skin	Erythema nodosum
	Pyoderma gangrenosum (see Fig. 4.3)
Liver and biliary tree	Sclerosing cholangitis
	Fatty liver
	Chronic hepatitis
	Cirrhosis
	Gallstones
Nephrolithiasis	
Venous thrombosis	

Information

Crohn's disease:

- Affects any part of GI tract, from mouth to anus
- 70% of cases affect the terminal ileum
- Can be controlled but not cured

Ulcerative colitis:

- Confined to colon
- Cured by colectomy
- Can affect the: rectum alone (proctitis), sigmoid and descending colon (left-sided colitis) or the whole colon (extensive colitis)

Both

- Extra-gastrointestinal manifestations, e.g. pyoderma gangrenosum (see Table 4.4 and Figure 4.3)



Figure 4.3 Pyoderma gangrenosum (courtesy of David Paige).

Further reading

Mowat C, et al. Management of Inflammatory bowel disease in adults. *GUT* 2011; **60**: 571–607 (BSG Guidelines).

ABDOMINAL PAIN

Most diseases of the GI tract are associated with abdominal pain but pain can also be referred to the chest or back. The characteristics of the pain can help in the diagnosis.

Case history

A 40-year-old man presents with epigastric and central abdominal cramping pain. For 48 h the pain has been continuous, severe and associated with vomiting. The pain does not radiate but it is getting worse by the hour.

On examination he has a temperature of 38°, pulse rate of 98 bpm. He has tenderness across the upper abdomen but no other signs. Bowel sounds are normal. He has no alteration of bowel habit and no loss of weight.

Immediate investigations

- Haematological: Hb, WCC, ESR
- Biochemical: U&Es, liver biochemistry, amylase
- Radiological: initial AXR for obstruction. CXR in acute pain for intestinal perforation.

Management

Develop the management plan to include:

- Symptomatic relief.
- Information for patient and relatives.
- Further investigations (endoscopy, ultrasound, CT and MRI as necessary to exclude perforation, obstruction, stones, calcification, cancer and ascites).
- Consultation with surgical colleagues.

In this case, abdominal pain situated in the epigastrium and central abdomen, and of the severity described, is always due to organic disease. Your differential diagnosis should include the following:

- An acute surgical cause:
 - Aortic aneurysm dissection
 - Appendicitis (even occasionally with upper abdominal pain)
 - Perforation
 - Intestinal obstruction.
- Acute pancreatitis:
 - Severe pain
 - Often associated with heavy alcohol use, gallstones, viral infection (e.g. mumps)
 - ↑ Serum amylase ($> 5 \times$ normal)
 - Gastric retention and vomiting
 - Ultrasonographic changes and contrast-enhanced dynamic CT (best investigation) show pancreatic swelling, necrosis and peripancreatic fluid collection.

Remember

Acute pancreatitis

Assessment of severity and poor prognosis (first 48 h):

- Age > 55 years
- Blood glucose > 10 mmol/L
- Serum urea > 16 mmol/L
- Serum calcium < 2 mmol/L
- Serum LDH > 600 U/L
- PaO₂ < 8 kPa
- WCC $> 15 \times 10^9$ /L
- Serum albumin < 30 g/L
- Serum AST > 200 U/L.

Symptom relief

Symptom relief depends on diagnosis. Use anti-spasmodics (hyoscine 20–40 mg \times 4/day). Minor analgesics (paracetamol) can help and NSAIDs are useful in some cases. When prescribing opiates (morphine, codeine) remember they can increase constipation and cause spasm in the sphincter of Oddi. Anti-emetics (metoclopramide 10 mg \times 2/day or prochlorperazine 5 mg \times 2/day) as necessary.

Patient information

This depends on diagnosis but should be delivered to both patients and relatives sensitively and with an understanding of underlying pathology.

- **Diagnosis and progress.** In this case, the 40-year-old patient turned out to have **acute pancreatitis**, with a serum amylase of 1000 units. He quickly settled by being nil by mouth and having IV fluids. The aetiology was never established but was thought to have perhaps been viral.

GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

Gastro-oesophageal reflux occurs normally. GORD occurs when the anti-reflux mechanism fails, allowing acidic gastric contents to make prolonged contact with the oesophageal mucosa.

Case history

A 48-year-old man was admitted with severe epigastric pain radiating up into his chest. He thought he had had a heart attack (see p. 284).

What investigations would you do on admission?

It is critical to exclude life-threatening conditions, such as myocardial infarction, pulmonary embolism and pneumothorax before labelling such pain as due to reflux.

Investigations

- FBC, liver biochemistry, serum amylase
- ECG, repeated after 1 hour
- CXR
- Cardiac markers, e.g. troponins and CPK

In this patient, two ECGs, CXR and cardiac markers (e.g. CPK, troponins) were normal. Additional features in the history included:

- Long history of reflux (GORD)
- Burning nature of the pain
- Flatulence
- A relationship of the present pain to previous similar pain
- A food-related element
- Exacerbation of pain with drinking hot liquids.

Features of gastro-oesophageal reflux

- Burning pain produced by bending, stooping or lying down
- Pain seldom radiates to the arms
- Pain precipitated by drinking hot liquids or alcohol
- Pain relieved by antacids.

Features of myocardial ischaemia

- Gripping or crushing pain
- Pain radiates into neck, shoulders and both arms
- Pain produced by exercise
- Accompanied by breathlessness.

Diagnosis of **GORD** was made in this patient from the history.

Progress and management

He was given liquid Gaviscon (10 mL) and a proton pump inhibitor (PPI, e.g. omeprazole 20 mg \times 2 daily for 6 weeks, reducing to 10 mg) to control the symptoms. Endoscopy will need to be performed in this man in view of his age.

Remember

- Reflux can be difficult to diagnose and although it is often associated with a hiatus hernia, more formal investigation might be necessary, e.g. endoscopy followed by oesophageal pH, impedance and pressure monitoring if necessary
- At endoscopy, assess degree of oesophagitis and check for Barrett's oesophagus (including biopsies).

BARRETT'S OESOPHAGUS

This occurs as a result of longstanding reflux. It consists of columnar epithelium with intestinal metaplasia extending upwards into the lower oesophagus and replacing normal squamous epithelium. Barrett's oesophagus (even short segment < 3 cm) is pre-malignant for **adenocarcinoma**. Risk factors for progression are male sex, age > 45 years, length of segment > 8 cm, early age of onset and duration of symptoms of GORD, the presence of ulceration and stricture and a family history. Dysplasia is patchy and biopsies from all four quadrants (every 2 cm) of the Barrett's segment must be performed. There is no evidence that treatment with PPIs or surgery leads to Barrett's regression. Patients without dysplasia do not require **surveillance**. Low-grade dysplasia requires regular endoscopic surveillance. High-grade dysplasia is now treated with radiofrequency ablation using the HALO system, but endoscopic ablation therapy with photodynamic therapy or laser is also used.

PEPTIC ULCER DISEASE

Case history (1)

In the clinic you see a 40-year-old man with epigastric pain that has been present on and off for a number of years. The doctor's letter indicates that the man has been a regular attender and has received antacids, H₂ receptor antagonists and a PPI at some time over the last 5 years. In 2005 the patient was found to have *H. pylori* antibodies in his serum and was given eradication therapy.

What should you do?

The history of intermittent epigastric pain is highly suggestive of peptic ulcer disease and you note there are no alarm features in the history. The patient has been given *H. pylori* eradication therapy but the GP has not

indicated the drugs that were used. The patient remembers taking two different tablets for 1 week. You ask about smoking (which delays ulcer healing) and also take a drug history. There is no history of NSAID or aspirin use.

Remember

Alarm features:

- Weight loss
- Anorexia
- Dysphagia
- Protracted vomiting
- Haematemesis or malaena

In the absence of alarm features it is reasonable to try a proton pump inhibitor if the history is suggestive of reflux, e.g. heartburn worse on bending.

What would you do next?

You would need to establish whether the patient has had successful *H. pylori* eradication.

Tests for *Helicobacter pylori*

- Serological IgG antibodies (useful in the community but does not distinguish between past or current infections).
- Urea breath tests (for current infections) measuring $^{13}\text{CO}_2$ (Fig. 4.4).

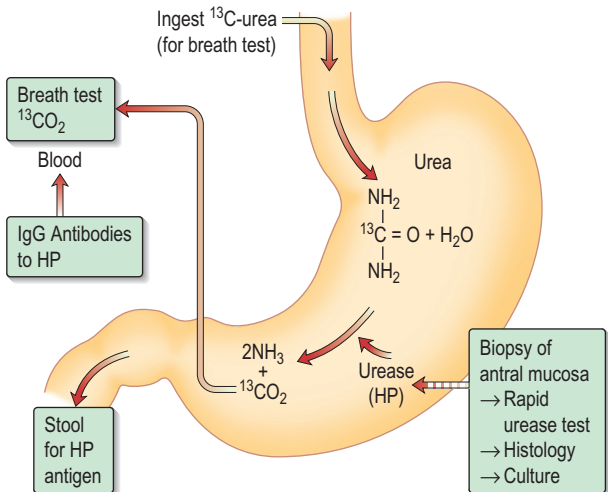


Figure 4.4 Metabolism of urea by *Helicobacter pylori* showing the different tests that are available for the detection of *H. pylori*.

- Antral biopsy: either for histology or for CLO (urease) testing (for current infections).
- Stool antigen test (current infection).

This patient's urea breath test is positive, indicating continuing *H. pylori* infection.

Treatment of *H. pylori* infection

Patients with peptic ulcer disease who are *H. pylori* positive should be given combination eradication therapy:

- Clarithromycin 500 mg twice daily for 1 week
- Amoxicillin 1 g twice daily for 1 week
- Omeprazole 20 mg twice daily for 2 weeks.

With increasing resistance to clarithromycin, quadruple therapy is now being used, as in this patient. He was given omeprazole 20 mg \times 2, tripotassium di-citrate bismuthate 120 mg \times 4, tetracycline 500 mg \times 4 and metronidazole 500 mg \times 3 – all daily for 2 weeks.

- **Progress.** This patient has had no further problems since his quadruple therapy and a stool antigen test was negative for *H. pylori*.

Case history (2)

You are asked by the cardiologists to see a man with epigastric pain. He has been admitted for urgent percutaneous coronary intervention (PCI). He is already on aspirin 75 mg daily. He has had many similar episodes of pain over the years. In 1988 he had an endoscopy and was told that he had an ulcer and was given Zantac. He points with one finger to his epigastrium as the site of his pain.

This is a classic history of duodenal ulcer disease.

What should you do?

As the PCI is tomorrow you recommend he is given a PPI, e.g. omeprazole 20 mg \times 2 daily and referred to gastroenterology outpatients.

The cardiology SpR would like to put the patient on anti-platelet therapy post PCI and is worried that he has an ulcer. This is a problem of balancing the risks. As the coronary stent is urgent they will have to go ahead with anti-platelet therapy with a cytoprotective PPI. The ideal situation for this man would be to perform endoscopy prior to PCI and if an ulcer is present, to heal his ulcer before the intervention.

After reassessment with the Consultant Cardiologist, it is still decided that the PCI is urgent and will go ahead despite its risks, which are fully discussed with the patient.

How do you investigate a patient with a suspected ulcer in the community?

- Less than 45 years: *H. pylori* serology. If positive, eradication therapy (see p. 48). If negative, treat symptomatically.
- Greater than 45 years: patients with new dyspepsia and those with alarm symptoms (e.g. anorexia, weight loss) should be referred for endoscopy.

Remember

- *H. pylori* serology can remain positive even after successful eradication of *H. pylori*
- Current *H. pylori* infection can be detected by the urea breath test (see Fig. 4.4), endoscopy (urease test, histology or culture) and detection of stool antigen.

Case history (2)

A 40-year-old woman was seen in the A&E department with a sprained ankle. She was sent home with a strapped ankle and given diclofenac to take for the pain. There was no history of indigestion. Ten days later she is brought in by ambulance having vomited blood. The bleeding was thought to be related to the NSAID therapy.

On examination she was not shocked and there are no signs of chronic liver disease. She had stopped bleeding and an endoscopy was performed in the next 24 h.

A bleeding ulcer, with a fresh adherent clot, was seen on endoscopy and was injected with adrenaline (epinephrine) 1:10 000 and a heater probe was also used. A biopsy was taken for *H. pylori*.

A bleeding ulcer might have certain stigmata that suggest rebleeding is likely to recur (see Remember box).

Gastric cancer does not usually cause an acute GI bleed; it is more likely to produce anaemia from chronic blood loss.

Remember

Stigmata of a recent bleed from an ulcer on endoscopy:

- Spurting vessel
- Prominent vessel
- Fresh adherent clot.

- **Progress.** The *H. pylori* test was positive, indicating chronic peptic ulcer disease. The haematemesis was precipitated by the NSAIDs.

Discharge policy

The patient's age, diagnosis on endoscopy, co-morbidity and the presence or absence of shock should be taken into consideration. In general, patients under the age of 60, as well as older patients who are haemodynamically stable and have no stigmata of recent haemorrhage on endoscopy, can be discharged within 24 h.

Note: All shocked patients need careful observation in hospital. Check your own hospital's guidelines.

Further reading

- Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection – the Maastricht IV/Florence consensus report. *Gut* 2012; **61**: 646–664.
- Managing acute upper GI bleeding. BSG Tool kit. *Lancet* 2011; **377**: 1048.
- Gralnek IM, Baskin AN, Bardon M. Management of acute bleeding from a peptic ulcer. *NEJM* 2006; **359**: 928–937.

IRON DEFICIENCY ANAEMIA

Case history

A 40-year-old, female, globe-trotting managing director was found at routine screening to have a haemoglobin of 80 g/L with an iron-deficient appearance on the film.

She admitted to some ankle swelling and increased breathlessness of recent onset. Examination was unhelpful.

FBC, film and low serum ferritin confirmed **iron deficiency**.

What do you do?

- Exclude all obvious causes of bleeding:
 - Heavy periods
 - Rectal bleeding
 - Recurrent nose bleeds.
- If there is no obvious menorrhagia, you can assume the anaemia is due to gastrointestinal disease. Malabsorption: coeliac disease is still very underdiagnosed.
- The patient travels a lot abroad and could have a bowel infestation. Remember hookworm is the most common cause of iron deficiency anaemia world-wide.
- Occult bleeding from the GI tract is common and can be confirmed by haemoccult testing. This, however, is totally unnecessary in a patient with iron deficiency because if there is no history of blood loss, blood can then only be lost from the GI tract.

Information

Faecal occult bloods:

- Of no use in males or post-menopausal females with iron deficiency anaemia and no other cause for bleeding
- Useful for screening populations for colonic cancer

What additional investigations are appropriate?

- Rectal examination is mandatory to exclude rectal cancer. Proctoscopy to exclude piles.
- Gastroscopy: peptic ulcer, gastric cancer and GORD can certainly occur in this age group. Also do a duodenal biopsy for coeliac disease (see Fig. 4.5).

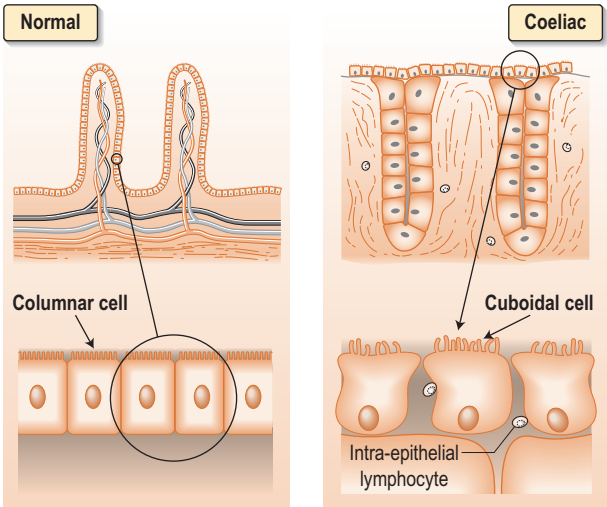


Figure 4.5 Small intestinal mucosa showing normal villi with normal columnar cells compared to coeliac mucosa showing subtotal villus atrophy, crypt hyperplasia, lamina propria inflammation and an increase in intra-epithelial lymphocytes.

Remember

Coeliac disease:

- Is increasingly recognised world-wide and has an incidence of less than 1:100 in many countries. Certain areas of the world are said to have a higher incidence, e.g. Ireland and Italy
- Malabsorption of iron as well as increased iron loss can occur. There might be other deficiencies as well, e.g. calcium and folic acid
- A history of steatorrhoea can be missed unless a detailed stool history is taken (*Note:* many patients do not have steatorrhoea or any gastrointestinal symptoms)
- Coeliac serology with anti-endomysial and anti-tissue transglutaminase (the target antigen for the endomysial antibody) antibodies. A serum IgA must be performed as these are IgA in vitro tests. Deaminated gluten peptide (DGP) testing is now becoming available. These tests have a high sensitivity and specificity.
- Diagnosis is confirmed by biopsy of duodenal/jejunal mucosa
- Treatment is with a gluten-free diet.

If gastroscopy is unhelpful, full colonic assessment is necessary. The best investigation is colonoscopy, which will allow full assessment of the colon when biopsy, polypectomy, laser treatment of angiodysplasia can be performed as appropriate.

If the above investigations are negative you have a problem. A small minority of patients fall into this category and the host of further investigations, performed with advice from the GI unit, will include:

- Small bowel follow-through
- Capsule endoscopy
- Enteroscopy
- Meckel's scan
- Angiography: preferably performed when a patient is bleeding and in this patient unlikely to be helpful
- Laparotomy with possibly simultaneous on-table endoscopy at the time.
 - **Progress.** This patient turned out to have menorrhagia due to fibroids, despite initially denying heavy periods.

Remember

- Iron deficiency anaemia in a post-menopausal female or any male with no obvious cause of blood loss must have a GI cause for the anaemia
- Few patients have an inadequate iron intake in developed countries.

Further reading

Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2000; 46 (Suppl IV): 1-5.

RECTAL BLEEDING

Rectal bleeding is characterised by the passage of fresh blood rectally as opposed to either occult loss when blood can only be detected by laboratory testing or melaena (see p. 66).

Case history

An 80-year-old woman was admitted in a shocked state after having passed 'a great deal' of fresh blood from her rectum. She gave no other history and prior to the incident had just returned on her bicycle from doing the shopping. Abdominal examination was normal.

How would you manage the patient initially?

- Establish IV infusion and give 0.9% saline
- Check Hb and U&Es
- Group and cross match blood
- Insert a CVP line
- Transfuse blood.

The patient stabilised and had no further bleeding.

Additional examination

Additional investigations must include a rectal examination, proctoscopy and rigid sigmoidoscopy.

Proctoscopy

This will allow the diagnosis of haemorrhoids and an anal fissure. These are the most common causes of rectal bleeding, but rarely if ever cause torrential blood loss. Features of bleeding from an anorectal lesion:

- Passage of blood after a motion, and not mixed with it
- Blood dripping into the pan
- Blood just on the paper
- Anal pain, particularly with an anal fissure.

Flexi sigmoidoscopy

This will determine the presence of a colitis and might show a lesion, e.g. carcinoma. If local anorectal disease is excluded, other causes include:

- Cancer
- Diverticular disease
- Colitis
- Angiodysplasia
- Polyps
- Ischaemia.
 - **Progress.** In this patient, sigmoidoscopy showed that the blood was coming from above the limit of the scope. Colonoscopy showed a bleeding polyp; this was excised.

Remember

Even in the presence of severe diverticular disease, a polyp and carcinoma can be the cause of the bleeding and must be excluded by colonoscopy.

FAMILY HISTORY OF COLON CANCER

Case history

A doctor phones to discuss a possible referral to the gastroenterology clinic. He has just seen an anxious, 32-year-old woman whose mother has recently died of colonic cancer. The patient has just discovered that her maternal aunt died of a similar complaint. The doctor emphasises that the patient herself has no GI symptoms.

What should you advise?

The patient needs to be seen by a gastroenterologist with a view to a full discussion on the pros and cons of having a colonoscopy.

Family cancer syndromes:

Familial adenomatous polyposis: multiple polyps are found throughout the colon and upper small bowel. All patients should be screened after

Table 4.5 Diagnostic criteria for hereditary non-polyposis colon cancer (HNPCC)

Modified Amsterdam criteria

- ← One individual diagnosed with colorectal cancer (or extra-colonic HNPCC-associated tumours) before age 50 years
- ← Two affected generations
- ← Three affected relatives, one a first-degree relative of the other two
- ← FAP should be excluded
- ← Tumours should be verified by pathological examination

Bethesda guidelines

- ← Colorectal cancer diagnosed in patient who is younger than 50 years
- ← Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, irrespective of age
- ← Colorectal cancer with the MSI-H ↑ histology ↑ diagnosed in a patient who is younger than 60 years
- ← Colorectal cancer diagnosed in one or more first degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age 50 years
- ← CRC diagnosed in two or more first or second degree relatives with HNPCC-related tumours, irrespective of age

MSI-H, microsatellite instability – high.

age 12 years because *all* patients will develop colon cancer unless the colon is removed.

Hereditary non-polyposis cancer of the colon (HNPCC) (Table 4.5): this accounts for 5–10% of colon cancers; the average age of diagnosis is 45 years. Cancers are mainly in the right-hand side of the colon.

A flexible sigmoidoscope can only reach 60–70 cm up the colon, where approximately 60% of cancers occur (Fig. 4.6).

The gastroenterologist advises a colonoscopy for this patient, which she agrees to have after full discussion.

Remember

Risks for development of colon cancer:

- Normal: 1:50
- With a first-degree relative: 1:17
- With an elderly first-degree relative: 1:30.

- **Progress.** This patient's colonoscopy showed a 2 cm polyp which was fully excised. Histologically this was a tubular adenoma and she was asked to return for a surveillance colonoscopy in 3 years' time. She was told that she would need continuous follow-up in view of the family history.

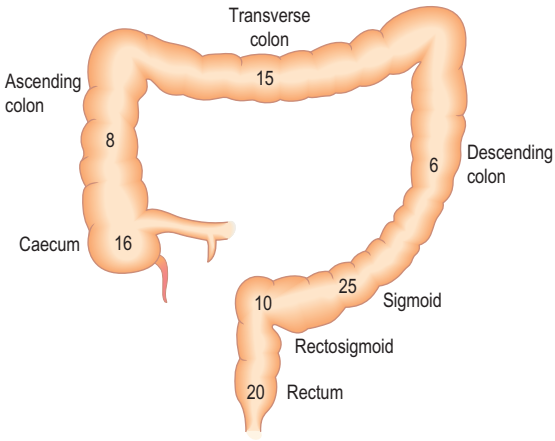


Figure 4.6 Distribution of colorectal cancer (%).

FUNCTIONAL BOWEL DISEASE

Case history

A 30-year-old woman is in the A&E department with severe lower abdominal pain. She is rolling around in agony but the surgical registrar has found no evidence of serious disease. He has already fully examined her and investigated her with routine blood tests and an abdominal X-ray, all of which are normal. Her boyfriend is aggressive and insisting that something must be done. The casualty officer is looking for help.

What do you do?

- Re-take the history with the possibility of this being irritable bowel syndrome (IBS).
- Re-examine the abdomen: think of all the causes of an acute abdomen again (see [Information](#) box).
- Review the investigations.

The history strongly supports the diagnosis of IBS. Remember that the pain can be very severe and real to the patient even though it is related to life events, i.e. the pain is not just 'all in the mind'.

Management

This can be very difficult, particularly because relatives often feel unable to cope. The situation needs to be calmed down with strong reassurance and pain relief (e.g. NSAID and anti-spasmodics). Refer to gastroenterology outpatients.

Information

Acute abdominal pain of sudden onset:

- Perforation, e.g. of a duodenal ulcer
- Rupture, e.g. aneurysm
- Torsion, e.g. ovarian cyst

Gradual onset:

- Inflammatory conditions, e.g. appendicitis, back pain

Think of:

- Pancreatitis
- Ruptured aortic aneurysm
- Renal tract disease

Liver and Biliary Tract Disorders

5

ABNORMAL LIVER BIOCHEMISTRY

'Liver function tests' are routinely requested.

Serum bilirubin, aminotransferases, alkaline phosphatase, γ -glutamyl, transpeptidase (γ -GT) and total proteins are measured. These are in fact tests of liver damage (hence the term 'liver biochemistry') rather than actual liver function. Liver function is assessed by serum albumin and the prothrombin time.

Case history

A doctor telephones you to ask whether a hospital referral is necessary for her patient. The doctor has recently seen a 55-year-old patient for a medical insurance examination for an American bank. She had found no problems with the patient at the time of the examination but the results of the liver biochemistry have come back abnormal. The tests showed:

- Serum bilirubin: 14 μ mol/L
- Serum alkaline phosphatase: 134 iu/L
- AST: 70 iu/L
- ALT: 90 iu/L.

What advice do you give?

These tests suggest intra-hepatic disease and you ask about the patient's alcohol history. The answer is only occasional alcohol. You suggest that the doctor could arrange the following tests while waiting for an outpatient appointment:

- Repeat LFTs
- Viral markers
- Serum autoantibodies
- Serum ferritin.

These tests will yield a diagnosis in most cases.

The doctor asks: would an ultrasound be helpful?

No. This is not the pattern of biliary or pancreatic disease.

You arrange to see the patient with your consultant in outpatients. At outpatients the history again is unhelpful. There is no history of:

- Blood transfusions
- Previous hepatitis
- IV drug use
- Sexual promiscuity.

On examination you notice a few spider naevi. The liver is not palpable.

The results of the tests performed by the doctor are now available (Table 5.1). HCV antibodies indicate **HCV infection** (chronic hepatitis) and the

Table 5.1 Further investigations into the cause of the abnormal liver function test

Test	Result	Implication
Repeat LFTs	Similar to above	
Hepatitis A	IgG positive IgM negative	Patient has been infected with HAV in the past or immunised. This virus does <i>not</i> cause chronic liver disease
HBsAg	Negative	See below
HCV antibodies	Positive	
Autoantibody screen	Negative	Positive titres usually found in autoimmune hepatitis
Serum ferritin	110 µg/L	This excludes hereditary haemochromatosis

Table 5.2 Significance of viral markers in hepatitis B

	Antigens
HbsAg	Acute or chronic infection
HbeAg	Acute hepatitis B Persistence implies: continuous infectious state development of chronicity increased severity of disease
HBV DNA	Implies viral replication (found in serum and liver; also present in HbsAg-negative patients due to mutant viruses)
Anti-HBs	Immunity to HBV; previous exposure or vaccination
Anti-HBe	Seroconversion
Anti-HBc	Acute hepatitis B (high titre)
IgM	Chronic hepatitis B (low titre)
IgG	Past exposure to hepatitis B (HbsAg-negative)

From Kumar and Clark *Clinical Medicine*, 8th edn, 2012.

patient will require HCV RNA, liver biopsy and possible treatment with anti-viral therapy with pegylated interferon and ribavirin, or with one of the newer protease inhibitors (boceprevir or telaprevir).

Armed with the HCV result you discuss IV drug use with your patient, who then admits to the very occasional use of IV drugs in the 1960s.

Although this patient did not have HBV, you need to know the significance of HBV markers (Table 5.2).

- **Progress.** This patient was referred to the Liver Clinic. Her HCV RNA showed 45 000 IU/ml viral load. She was treated with pegylated interferon and ribavirin and at 3 months she had a good response with a 2 log reduction in RNA. She stopped therapy at 6 months and continued to be followed up in the clinic.

JAUNDICE

Jaundice is detected clinically when the serum bilirubin is greater than 50 $\mu\text{mol/L}$ (3 mg/dL).

Case history (1)

A 45-year-old woman has been admitted to MAU with deep jaundice. She gives a history of two episodes of severe abdominal pain which had lasted for about half an hour. She has lost her appetite and consequently lost some weight.

Abdominal examination is unhelpful; there were no signs of chronic liver disease.

The blood tests showed a raised serum bilirubin, an ALT of 50 units and a high alkaline phosphate of 410 units. You order an ultrasound examination of the liver and biliary tree as you suspect that she has got gallstone disease (Fig. 5.1).

Investigations

- Blood count, liver biochemistry
- Liver function (INR and albumin)
- Abdominal ultrasound
- Viral markers to exclude hepatitis causing intra-hepatic cholestasis

Ultrasound in extra-hepatic obstruction can show:

- Dilatation of the intra-hepatic biliary tree
- Dilatation of the common bile duct
- Gallstones in the gall bladder
- Gallstones in the biliary tree
- A pancreatic mass
- Metastatic liver disease.

In this patient, the ultrasound showed gallstones in the gall bladder and a dilated common bile duct. Provided this patient's clotting is satisfactory, the next procedure should be an ERCP. This would enable a better visualisation of the system and would allow a gallstone that is causing the obstruction in the common bile duct to be removed. A sphincterotomy would need to be performed beforehand and the stone could be removed with a basket or a balloon. If the stone is very large, the stone can be crushed and the debris removed. In an elderly patient, stent insertion to maintain drainage is an option.

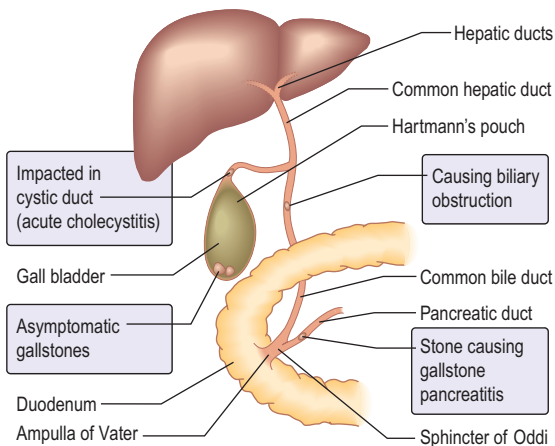


Figure 5.1 Clinical presentation of gallstones.

- **Progress.** In this patient the stones were cleared from the common bile duct at ERCP and this was followed by a laparoscopic cholecystectomy.

Remember

- Cholangitis often accompanies gallstones obstructing the biliary tree and urgent duct drainage should be performed. Antibiotics (e.g. ciprofloxacin 500 mg \times 2) should be given.
- The residual stones are removed endoscopically when the patient has recovered.

Case history (2)

A 78-year-old man is admitted with marked jaundice. He was previously fit and well but the ultrasound arranged by his doctor showed a dilated biliary system with the probability of a pancreatic mass.

An endoscopic ultrasound and/or CT scan should be performed to assess the vague possibility of operability.

An ERCP with placement of a stent through the stricture enables drainage and is the usual treatment. This makes the patient feel a lot better as well as relieving the jaundice. This was performed in this man.

Jaundice without pain is quite common with carcinoma of the pancreas but with gallstones there is usually a history of biliary pain accompanying the jaundice.

A similar obstruction could equally well be related to an obstruction higher up in the duct system, perhaps due to a cholangiocarcinoma. This could arise in pre-existing sclerosing cholangitis, although this would usually occur at a younger age.

Complications of ERCP sphincterotomy (complication rate 8–12%)

- Bleeding (severe in 2%)
- Perforation
- Acute pancreatitis (5%)
- Cholangitis.

Case history (3)

A 20-year-old woman is admitted in a confused state and deeply jaundiced. She has recently returned from India, where she had been trekking; she had had a major argument with her boyfriend. A subconjunctival haemorrhage was noticed on examination.

This patient is critically ill with fulminant hepatic failure and it is essential to stabilise her as soon as possible.

A central venous line was inserted and as her haemoglobin was very low, she was given 2 units of red blood cells. The clotting studies give an indication of the degree of damage to her liver, and will be useful for daily follow-up. It is also necessary to make sure that the patient's potassium and blood sugar are satisfactory and whether replacements are necessary.

Investigations

- Haemoglobin
- Clotting studies and albumin
- Liver enzymes
- Blood sugar
- U&E

This woman's investigation showed a bilirubin of 130 $\mu\text{mol/L}$, ALT 900 U/L, AST 785 U/L, alkaline phosphatase 109 U/L, albumin 34 g/L, INR 2.2, indicating **severe hepatocellular damage**.

Further management

This patient is liable to infection and intravenous antibiotics are required after blood cultures have been taken.

Remember

Hepatic encephalopathy should be treated with a low-protein diet and lactulose.

It is essential to try to establish a cause of this patient's jaundice. This might be hepatitis A or hepatitis E – both are endemic causes of hepatitis in India and often follow an initial respiratory type of illness; they can occasionally cause fulminant liver damage. A paracetamol overdose is also a possibility, as her boyfriend said that she was very upset when they returned to the UK.

Further investigation

Viral markers for the above causes, and paracetamol levels, must be obtained urgently. Other investigations would include the following if no cause has been found:

- Autoantibodies
- Copper studies
- Alpha-1 anti-trypsin levels.

In this case, the patient's relatives arrive and say they have found empty containers labelled paracetamol 500 mg tablets in her bedroom at her apartment.

The patient might well stabilise at this stage but a close eye will need to be kept on her for potential infections, particularly with opportunistic organisms. It is reasonable to give Acetylcysteine in the initial management of such comatosed patients, whether or not the paracetamol blood level is high.

This patient's clinical condition deteriorated, with a modified early warning score (MEWS) score of 5. She became increasingly drowsy and confused and developed a flapping tremor and fetor hepaticus. Her investigations now showed a serum bilirubin of 320 $\mu\text{mol/L}$, ALT 4200 U/L, AST 3800 U/L, serum albumin 32 g/L, with an INR of 3.62. Urgent advice was sought from the nearest liver unit.

Information

Criteria for transfer to a specialised unit:

- INR > 3.0
- Presence of hepatic encephalopathy
- Hypotension after resuscitation with fluid
- Metabolic acidosis
- Prothrombin time (seconds) > interval (hours) from overdose (in paracetamol cases)

You arrange for transfer. In specialised units 70% of patients with paracetamol overdose and grade IV encephalopathy survive. Factors that indicate a poor prognosis with paracetamol overdose (without transplantation) are:

- Arterial pH < 7.3 OR
- Serum creatinine > 300 $\mu\text{mol/L}$
- Prothrombin time > 100 s
- Grade III-IV encephalopathy.
 - **Progress.** This woman was seriously ill with acute hepatic failure. She survived with supportive therapy without transplantation being necessary.

ACUTE LIVER DISEASE

Case history

A medical student turns up in A&E with jaundice. He is very worried that he has gallstones and might need surgery. He has never seen jaundice outside a surgical ward.

How do you approach this situation?

First, you point out that gallstones are rare in a young person and that a viral hepatitis is, by far and away, the most likely diagnosis. You quickly ascertain that he has been previously immunised against hepatitis B and only drinks beer after rugby. He denies IV drug use. Your thoughts now turn to how he acquired hepatitis A. There is no clue from the history:

- No contacts with jaundice
- No prodromal features
- No travel abroad.

On examination, apart from jaundice, there are no other abnormal signs.

Take blood for:

- Liver biochemistry
- HAV IgM (to indicate acute HAV infection).

You tell him to go back to his student flat, be careful with his personal hygiene and return in 2 days for his results (Table 5.3).

Oops! HAV IgM negative! You realise that although hepatitis A is very, very common in such a situation there are other causes. You had omitted to take a careful drug history from someone you knew (NB: remember Ecstasy!).

- **Progress.** This student turned out to have glandular fever (EBV infection), which can occasionally present with jaundice.

Table 5.3 Test results in acute liver disease

Test	Result	Implication
Serum bilirubin	70 $\mu\text{mol/L}$	
AST	300 iu/L	Compatible with acute
ALT	280 iu/L	hepatitis
ALP	140 iu/L	
HAV IgM	Negative	

ASCITES

Ascites is fluid within the peritoneal cavity due to sodium and water retention, e.g. cirrhosis or heart failure or secondary to malignant deposits.

Case history (1)

A 45-year-old woman presents with ascites gradually increasing over 2 weeks.

Examination shows no abnormality outside the abdomen.

Determining the cause of the ascites is essential to developing a management plan and she is admitted to MAU.

Investigations

- Liver biochemistry
- FBC
- INR and serum albumin
- Ascitic tap – for white cell count, culture, protein, malignant cells

Information

Paracentesis (ascitic tap):

- Obtain the patient's consent after explaining procedure
- Percuss the dull area in the RIF
- Clean the skin and inject local anaesthetic (1% lidocaine) into skin using orange needle
- Insert 21-gauge needle (green) on a 20 mL syringe into the fluid
- Withdraw approximately 20 mL
- Withdraw the needle and apply dressing

Ascitic fluid

The ascitic protein concentration, as well as the serum : ascites protein gradient (SAG) help differentiate a transudate (< 25 g/L or SAG > 11 g/L) from an exudate (> 25 g/L or SAG < 11 g/L).

In this case, a high ascitic protein (> 25 g/L) suggests tumour or infection.

Malignant cells were present; further imaging with ultrasound – abdominal and pelvic – CT were performed to determine tumour site.

- **Diagnosis.** In this patient, the age and sex suggested an **ovarian malignancy** and this was confirmed.
- **Progress.** She was referred to the Gynaecology Department for further management.

Case history (2)

A 45-year-old man has attended his doctor on many occasions with alcohol-related problems. He is sent up to A&E with a swollen abdomen. He admits to drinking 60–80 units per week for 20 years.

On examination he is not jaundiced, but he has spider naevi, liver palms, Dupuytren's contractures and testicular atrophy. He has gross ascites and pitting ankle oedema.

What should you do?

Investigations

- Liver biochemistry
- FBC
- Serum albumin and INR
- Urea, creatinine, eGFR and electrolytes

An ascitic tap is necessary to rule out infection and malignancy, even though he has **chronic liver disease**.

Ascitic fluid showed 25 cells/mm³, protein content of 23 g/L, with a serum ascitic albumin gradient of < 9 g/L, i.e. a transudate.

- A transudate (< 25 g/L) indicates cirrhosis without any complication.
- In a patient with known liver disease, a high white cell count and high protein levels suggest infection (spontaneous bacterial peritonitis).

Remember

Think of TB in ethnic minorities.

Ultrasound of the liver and spleen is now performed. It shows splenomegaly (portal hypertension) and an irregular liver with fat, indicative of cirrhosis.

Immediate management

- Bed rest
- Salt restriction
- Daily weights and U&Es.
- Start diuretics – spironolactone 100 mg/day (increasing gradually to 400 mg/day) to obtain a weight loss of 500 g/day
- If inadequate response to above, introduce furosemide 40–120 mg/day
- Give thiamine 25–50 mg daily.

The patient *must* stop drinking.

Subsequent management

It may be necessary to do a liver biopsy to confirm the cause of cirrhosis, but only after the ascites is removed. If it is impossible to do a percutaneous liver biopsy (due to ascites, prolonged clotting), then biopsy can be undertaken through the jugular vein under X-ray control.

- **Progress.** This patient was referred to the Alcohol Dependency Unit after resolution of his ankle swelling and ascites. He may require liver transplantation and he should be referred on to a Liver Unit for assessment. He continues to abstain from alcohol but at present he does not fit the criteria for transplantation (MELD Score 7).

Further reading

Moore KP, Wong F, Gines P, et al. Management of ascites in cirrhosis. Report on the consensus conference of the International Ascites Club. *Hepatology* 2003; **38**: 258–266.

Remember

Liver disease with few cutaneous or other signs of liver disease can occur particularly in chronic hepatitis C.

HAEMATEMESIS AND MELAENA

Haematemesis is vomiting blood. Melaena is the passage of black, tarry stools, usually from a lesion proximal to the right colon.

Case history

A 70-year-old man was admitted, having vomited blood this morning. His stools have been loose and black (melaena).

On initial assessment he looked pale and was shocked, with a tachycardia of 110 beats/min and a BP of 80/60.

An IV cannula was immediately inserted, blood taken for Hb, urea and electrolytes, clotting, grouping and cross matching for 4 units. He was initially given fluid replacement with a colloid.

Resuscitation

- IV access
- CVP assessment
- Fluid replacement (initially with colloid)
- Blood transfusion
- O₂ for shocked patients.

Remember

Hb < 100 g/L, urea ↑, postural hypotension present, pulse rate 110/min. This patient is severely compromised and needs urgent treatment.

The gastroenterologists and surgical teams were informed. He was admitted to the high-dependency unit, a CVP line was inserted.

Many hospitals have multidisciplinary teams and protocols. Keep the patient nil by mouth until the bleeding has stopped. Causes of upper gastrointestinal bleeding are shown in Figure 5.2.

A further history of this man revealed that he had a high alcohol intake of 70 units/week for many years. He had no history of long-term dyspepsia and did not take NSAIDs, including aspirin.

On examination he had signs of chronic liver disease with spider naevi and gynaecomastia. His liver was 4 cm palpable and he had splenomegaly.

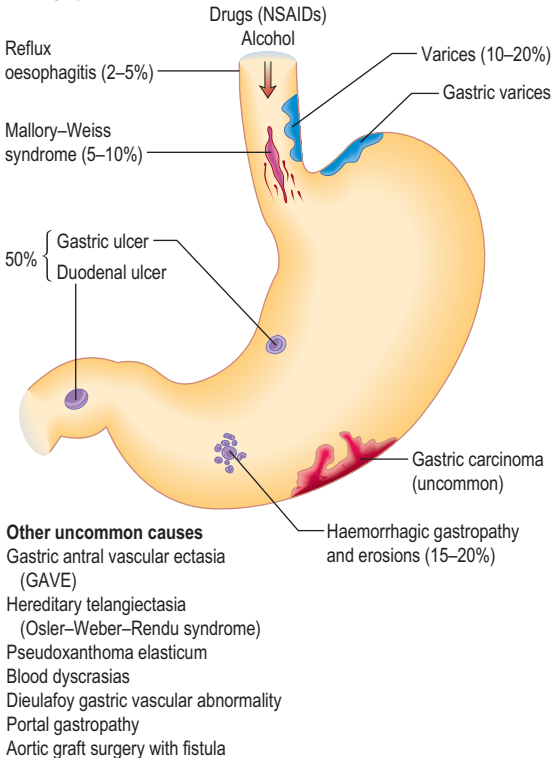


Figure 5.2 Causes of bleeding.

Remember

Shock:

- Pallor
- Cold nose
- ↓ Systolic BP.

The common causes of a GI bleed are

- Oesophageal varices
- Peptic ulcer
- Gastric cancer
- Gastric erosions.

Management

His haemoglobin returned as 90 g/L and the urea was raised at 10 mmol/L. A blood transfusion was started to resuscitate him (Fig. 5.3). On improvement he had an endoscopy which showed oesophageal varices and these were banded (Fig. 5.4). On return to the ward he had a further haematemesis 4 hours later. Vasoconstrictor therapy was given.

Vasoconstrictor therapy

The main use of this is for emergency control of bleeding whilst waiting for endoscopy and in combination with endoscopic techniques. The aim of vasoconstrictor agents is to restrict portal inflow by splanchnic arterial constriction.

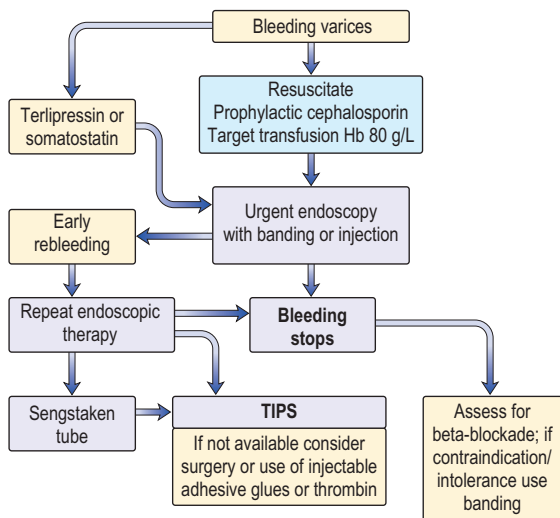


Figure 5.3 Management of gastrointestinal haemorrhage due to oesophageal varices. TIPS, transjugular intrahepatic portosystemic shunt.

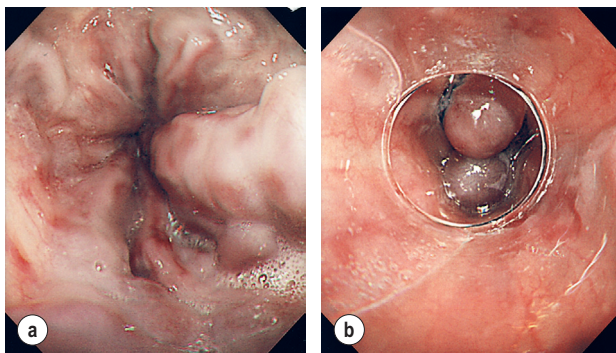


Figure 5.4 Oesophageal varices (a), with band in place (b). (Kumar and Clark *Clinical Medicine* 8th edn, 2012, p. 333).

- **Terlipressin.** This is the only vasoconstrictor shown to reduce mortality. Dose is 2 mg 6-hourly, reducing to 1 mg 4-hourly after 48 hours if a prolonged dosage regimen is used. It should not be given to patients with ischaemic heart disease. The patient will complain of abdominal colic, will defecate and have facial pallor owing to the generalised vasoconstriction.
- **Somatostatin.** This drug has few side effects. An infusion of 250–500 µg/h appears to reduce bleeding, but has no effect on mortality. It should be used if there are contraindications to terlipressin.

Balloon tamponade with a Sengstaken–Blakemore tube can be used if the bleeding continues. Use the gastric balloon only initially but, if the bleeding is not controlled, inflate the oesophageal balloon, remembering that continuous inflation leads to oesophageal damage. It has serious complications and should be left in situ for only 24 h.

If these measures fail, transjugular intra-hepatic portosystemic shunt (TIPS) might be required and is often used as the treatment of choice for gastric varices.

- **Progress.** Unfortunately this patient continued to bleed, despite a repeat endoscopy with injection of the varices. A Sengstaken–Blakemore tube was put in place and he was therefore referred urgently on to a liver unit for TIPS insertion.

Remember

Erosions can bleed profusely and be very difficult to control.

Further reading

Jalan R, Hayes PC. UK Guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2000; **46** (Suppl 3–4): III1–III15.

LIVER FAILURE

Case history

A 60-year-old female has been a known user of alcohol for the past 20 years. She is admitted because of deterioration in her health with confusion and the development of ascites.

Further history indicates that she has stopped drinking some 2 months ago and suffered no withdrawal symptoms.

On examination you wonder whether she has liver failure.

What signs indicate liver failure?

- Jaundice
- Ascites/portal hypertension (splenomegaly)
- Hepatic encephalopathy:
 - Hepatic flap
 - Fetor hepaticus
 - Constructional apraxia
- Signs of chronic liver disease, e.g.:
 - Spider naevi
 - Gynaecomastia
 - Dupuytren's contracture
 - Liver palms.

If there is no risk of bleeding, then concentrate on determining the level of encephalopathy:

- Grade 1: disorientated
- Grade 2: confused
- Grade 3: comatose
- Grade 4: unconscious.

Early signs should be demonstrated by asking the patient to copy a five-pointed star.

Information

Portosystemic encephalopathy (PSE) is a neuropsychiatric syndrome that occurs in cirrhosis. The blood by-passes the liver via collaterals allowing 'toxic' metabolites to pass directly to the brain. The nature of these 'toxins' is unclear but appear to be related to ammonia. Treatment is aimed at reducing protein breakdown in the gut.

Immediate management

- Measure electrolytes and blood sugar (BS), liver function and liver biochemistry.
- Ascitic tap to rule out infection (p. 64).
- Low protein and low salt diet.
- Thiamine.

- Establish infusion of 5% glucose (10% if BS is low).
- Diuretic therapy (see ascites).
- Use purgatives: lactulose 10–20 mL × 3/day to produce two to three stools a day.
- Determine presence of infection both in ascites (ascitic tap) and systemically (blood culture) and treat.

Further management

Monitor daily:

- Weight (see ascites)
- Conscious level (Glasgow Coma Score)
- Liver function tests and coagulation
- Electrolytes and blood sugar.
 - **Progress.** This woman's condition improved dramatically and she was ready for discharge from hospital after 10 days. She was referred to the Alcohol Dependency Unit and regular follow-up arranged at the Liver Clinic.

EXCESS ALCOHOL USE

Case history

A 45-year-old man presents with a history of excessive alcohol intake for 10 years since his marriage failed. He has sought help from counselling services but has been unable to remain sober. His presenting symptoms were of collapses in the street and home – the most recent collapse was witnessed and reported as epileptic.

Neurological examination shows that he is conscious, aware of his surroundings but confused (GCS 13). He has nystagmus and ataxia when asked to walk. **Examination of his legs** shows diminished sensation to light touch, pinprick and vibration below the knees. Ankle jerks are absent.

This man has two features of excess alcohol consumption.

1. Central findings – Wernicke–Korsakoff syndrome. This is sometimes reversible with parenteral thiamine therapy.
2. Peripheral neuropathy which is usually not reversible on alcohol abstinence or vitamin therapy.
 - **Management.** Start intravenous vitamins immediately – parenteral vitamin B and C should be used for the first 3 days. *Note:* Serious, allergic adverse reactions can occur. Give injections slowly and know how to treat anaphylaxis. Thiamine 100 mg × 3 day given orally throughout admission.

Information

Epilepsy occurs in 3–10% of patients who have alcohol dependence associated with:

- Alcohol intoxication
- Alcohol withdrawal
- Hypoglycaemia

A full history and examination must be undertaken to exclude:

- Neurological damage (central, peripheral)
- Hepatic damage/signs of liver failure
- Use of other drugs

Further treatment

- Withdraw all alcohol.
- Sedate: use benzodiazepines in adequate doses to produce sedation but beware of respiratory depression.
- Keep under supervision.
- Do not mix sedatives.
- Reduce diazepam slowly over next 5 days, observing resolution of signs of withdrawal:
 - Sweating
 - Shaking
 - Vomiting
 - Agitation
 - Hallucination.
- Do not use anti-epileptics.

Further management

Seek help from agencies dealing with alcohol and drug use for assessment and further management. Following abstinence, give Acamprosate 666 mg × 3 daily. This drug acts by enhancing GABAergic inhibition.

Lesser degrees of damage than in the above case can occur in excess alcohol use and must always be assessed in all patients attending hospital. These findings are commonly hidden and should be sought using a non-judgemental interviewing style.

Additional biochemical tests can help to determine physical damage produced by alcohol (MCV, triglycerides, uric acid, γ -GT).

Remember

There are many initiating factors for alcohol excess. It produces damage in many areas of function – financial, social, psychological and physical – and all need addressing.

- **Progress.** This man was discharged from hospital with regular attendance at the Alcohol Dependence Unit. His attendance became erratic and he started drinking again.

CHOLECYSTITIS

Case history

A 28-year-old man presents to the A&E Unit with right hypochondrial pain. This has been persistent, increasing in severity over the last three days.

On examination there is right hypochondrial tenderness. In view of his age and general good health he is sent home after surgical review, given paracetamol and told to see his doctor for follow-up.

Two days later a rather concerned doctor phones A&E to say that the patient's pain has persisted and the tenderness is marked. You ask him to send him back to A&E. **On examination** you confirm the doctor's findings of marked tenderness in the right hypochondrium. He has a temperature of 37.8°C.

What should you do now?

In view of the persistence of pain and second referral by his doctor, admit the patient to the medical assessment unit. Do the blood tests shown in the investigations box.

Investigations

- FBC
- U&Es
- Liver biochemistry
- Serum amylase
- Blood culture in view of pyrexia

One hour later your house officer phones you to say his WCC is 19 000. Clearly he has an infection and you tell your house officer to organise an urgent ultrasound while you call the surgical registrar. The surgical registrar recognises the patient he discharged 2 days ago. You discuss possible diagnoses. The ultrasound scan (Fig. 5.5) shows:

- Gallstones in the gall bladder
- Sonographic Murphy's sign
- Gall bladder wall thickening
- Peri-cholecystic fluid.

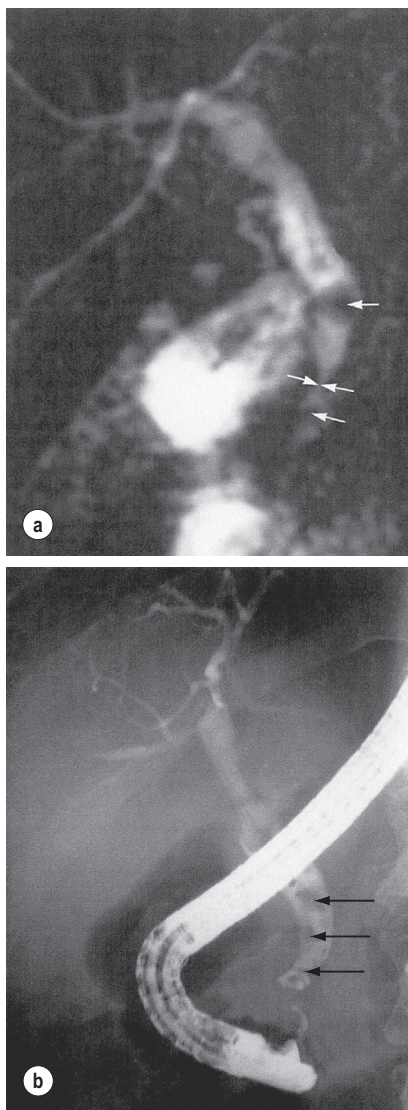


Figure 5.5 Ultrasound scan in a patient with acute cholecystitis. There is a stone (casting an acoustic shadow – thin arrow) impacted in the gall bladder neck, with a distended gall bladder (thick arrow) and thickening and oedema of the gall bladder wall.

Diagnosis

Remember

- Acute appendicitis: but the site of pain is a bit high
- Acute cholecystitis: but the patient is 28 years old and a man – surely not!
- A localised perforation and other mischief run through your mind.

The diagnosis is **acute cholecystitis**. The surgical SpR starts antibiotics (a cephalosporin, e.g. cefuroxime), nil by mouth and IV fluids. He books him for a laparoscopic cholecystectomy in 2 days' time.

Remember

Gallstones can occur at any age and not necessarily in fair, fat, fertile females of forty! Always think of appendicitis in a young patient with acute pain. Ultrasound/CT scans are invaluable in making the diagnosis.

- **Progress.** A successful laparoscopic cholecystectomy was performed with no complications.

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MICROCYTIC AND MACROCYTIC ANAEMIA**Definition of anaemia**

Anaemia is present when the level of haemoglobin in the blood is below the normal range. The normal range varies at different ages and between men (130–180 g/L) and women (115–155 g/L).

Remember

An accurate result depends on a correctly taken blood sample:

- Avoid prolonged venous occlusion
- Don't take the sample from an arm with an IV infusion

If the haemoglobin concentration doesn't fit the clinical picture take another sample.

Assessment

The impact of anaemia on an individual is variable and will depend on:

- The degree of anaemia
- The speed of onset
- Age
- Cardiovascular reserve.

Symptoms are non-specific and clinical signs easily overlooked:

- Tiredness, lack of energy
- Shortness of breath on exercise
- Palpitations
- Ischaemic pain.

Investigations

The classification of anaemia (Fig. 6.1) is based on the mean red cell volume (MCV; NR 76–96 fL).

Further investigation is determined by whether the anaemia is microcytic (< 76 fL), macrocytic (> 96 fL) or normocytic.

What is the reason for her anaemia and is it relevant to her presentation?

The first thing to exclude is iron deficiency, commonly due to uterine or gastrointestinal bleeding. Iron deficiency is unlikely in this patient:

- Very low MCV with only moderate anaemia
- Minimal variation in red cell size (anisocytosis) and shape (poikilocytosis).

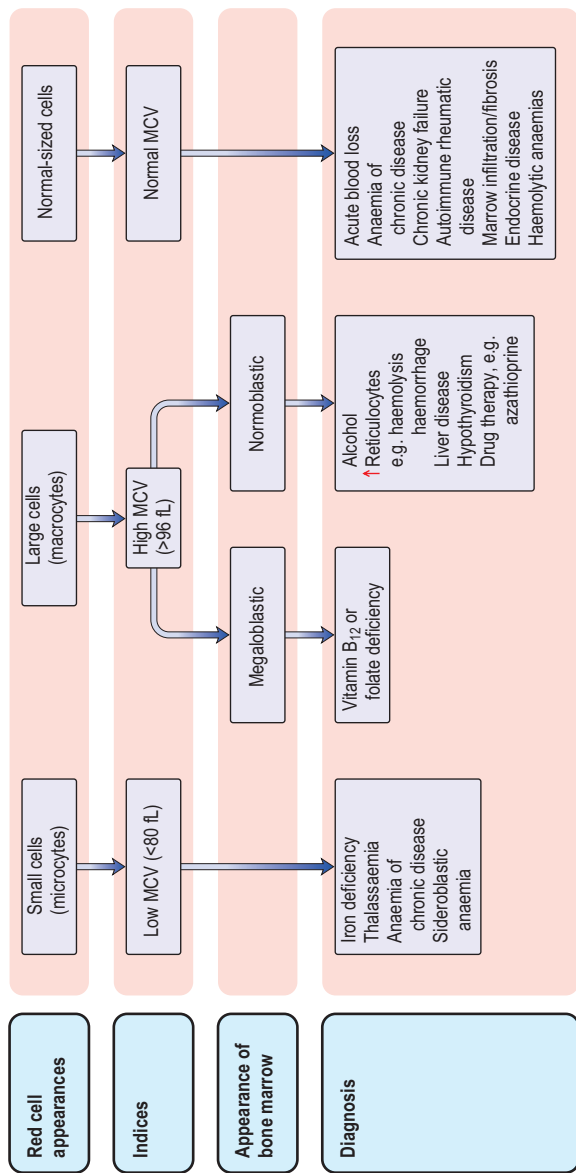


Figure 6.1 Classification of anaemia. MCV, mean corpuscular volume.

Case history (1)

A 45-year woman of African origin presents to the A&E department with chest pain that is thought to reflect cardiac ischaemia.

On examination she looked well. CVS examination showed a pulse of 82/min, a blood pressure of 140/80 and no abnormal signs. General examination was normal.

Investigations

- Hb 99 g/L
- MCV 59 fL
- RDW 14%
- WBC $6.4 \times 10^9/L$
- Platelets $273 \times 10^9/L$
- ESR 10 mm/h
- Anisocytosis, poikilocytosis +
- Target cells ++

These are the features of a microcytic anaemia.

- The serum ferritin ($30 \mu\text{g/L}$) was normal, indicating normal tissue stores of iron (**Note:** ferritin can be high because it is an acute-phase protein that rises whenever the ESR or CRP is elevated).

The anaemia of chronic disorder, a form of functional iron deficiency, is also unlikely without an obvious underlying illness and a normal ESR.

Remember

- Ferritin is an acute-phase protein. Iron deficiency can therefore be difficult to diagnose in the presence of inflammatory disease and tissue iron stores might need to be examined directly by bone marrow aspiration
- Serum transferrin receptor assay does differentiate between these conditions (see p. 142).

A common cause of a microcytic anaemia in patients of certain ethnic groups is β -thalassaemia trait. This is common in people from Africa, the Mediterranean, the Middle East, India and south-east Asia.

Characteristically, β -thalassaemia trait results in a marked microcytosis with only a moderate anaemia, as shown in this patient. In addition, the red cell distribution width (RDW) is normal (NB - it is high in iron deficiency).

β -thalassaemia trait is confirmed by measuring HBA₂, which is normally < 3.4% of total haemoglobin.

- **Progress.** The HBA₂ in this patient was 5.2%, confirming a diagnosis of **β -thalassaemia trait**.

Patients are asymptomatic and require no treatment. **Note:** Do not give iron. The anaemia is not contributory to this patient's cardiac ischaemia. The patient was referred to the Cardiac Department for investigation and management of her chest pain.

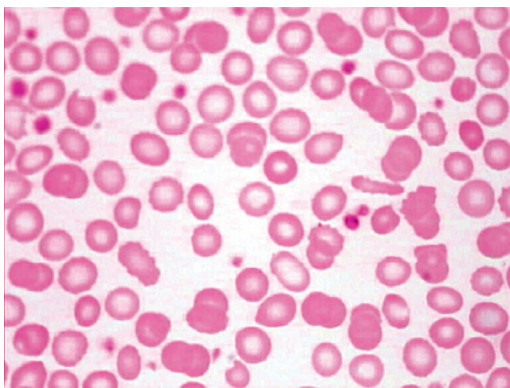


Figure 6.2 Typical blood film in chronic iron deficiency anaemia. Note the pale red cells with pencil (elongated) cells.

Remember

The anaemia of β -thalassaemia trait is:

- Life-long
- Stable.

Iron deficiency anaemia

Iron deficiency anaemia (Fig. 6.2 and see p. 142) responds to treatment with oral iron supplements – ferrous sulphate 200 mg \times 3 daily (or all in one dose) for 6 months – it is essential to give a full course of treatment. Lower the dose if GI symptoms occur. Parenteral therapy is required only rarely. The cause of iron deficiency is almost always blood loss and the cause **must** be determined.

Other causes include:

- Poor diet
- Multiple pregnancies
- Regular blood donation.

Further reading

Provan D. Mechanisms and management of iron deficiency anaemia. *British Journal of Haematology* 1999; **105** (Suppl 1): 19–26.

Case history (2)

An 81-year-old woman presents to the A&E department with recent onset congestive cardiac failure.

On examination she is mildly jaundiced and anaemic. Her pulse was 88/min, BP 120/90. She had signs of heart failure with a

Case history (2) (continued)

raised venous pressure, a 3rd heart sound, basal crackles and marked lower leg oedema.

Investigations

- Hb 32 g/L
- MCV 121 fL
- WBC $1.5 \times 10^9/L$
- platelets $64 \times 10^9/L$
- aniso poikilocytosis + + +
- hypersegmented neutrophils present

The findings indicate a severe macrocytic anaemia with a moderate neutropenia and thrombocytopenia. The diagnosis could be pernicious anaemia.

Vitamin B₁₂ or folate deficiency impairs DNA synthesis and affects all rapidly dividing cells, particularly in the bone marrow, resulting in pancytopenia when severe. The anaemia is slow to develop and elderly patients, in particular, often do not present until very late.

Avoid blood transfusion, if at all possible, because there is a risk of volume overload and acute left ventricular failure.

Make a precise diagnosis by measuring serum vitamin B₁₂, serum and red cell folate:

- In vitamin B₁₂ deficiency the serum vitamin B₁₂ concentration is always reduced; in folate deficiency the red cell folate concentration is always reduced.
- Severe vitamin B₁₂ deficiency can be associated with a low red cell folate and a normal or high serum folate. Vitamin B₁₂ is required to polyglutamate folate, without which folic acid cannot be retained within cells.

Remember

Drugs and rare metabolic defects can result in megaloblastic anaemia with normal vitamin levels:

- Methotrexate induces functional folate deficiency
- Transcobalamin II deficiency results in intracellular vitamin B₁₂ deficiency (but is very rare).

Bone marrow aspiration (not generally necessary since modern analysers can provide rapid vitamin B₁₂ levels):

- Confirms megaloblastic erythropoiesis
- Documents pretreatment iron stores
- Excludes other conditions – myelodysplasia, acute leukaemia and aplastic anaemia – all of which can present with a macrocytosis and pancytopenia.

Causes

- **Folate deficiency?** Nutritional deficiency is almost always a factor in any cause of folate deficiency, whether this is due to increased

requirements (e.g. myelofibrosis, haemolysis) or to excess alcohol use. In malabsorption, e.g. coeliac disease, there is also poor dietary intake of folate.

- **B₁₂ deficiency?** Most cases of vitamin B₁₂ deficiency are due to malabsorption, either gastric (because of intrinsic factor deficiency) or intestinal (due to small bowel disease). Pernicious anaemia (antibodies against intrinsic factor) is the most common cause.

Additional investigations

- Intrinsic factor antibody assay (positive in 50% of patients with pernicious anaemia).
- Anti-tissue transglutaminase antibodies and/or jejunal biopsy (to exclude coeliac disease).
- Barium meal and follow-through (to exclude small bowel disease, e.g. Crohn's disease); in a woman of this age only after the other causes have been excluded.

Many patients with moderate vitamin B₁₂ or folate deficiency have a normal haemoglobin with a raised MCV. Vitamin assays should be performed if the clinical picture is suggestive of a deficiency picture.

- Gastrointestinal disease or surgery including glossitis, malabsorption or diarrhoea
- Neurological disease, including visual loss, a peripheral neuropathy or evidence of demyelination
- Psychiatric disorders including dementia, confusion or depression
- Malabsorption or restricted diets, including vegans and those with anorexia nervosa
- Alcohol excess
- Infertility
- Autoimmune endocrine disease
- Family history of pernicious anaemia
- Drug therapy, particularly anti-convulsants.
 - **Diagnosis.** This patient had megaloblastic anaemia secondary to severe vitamin B₁₂ deficiency.

Pernicious anaemia

- Serum B₁₂: 25 ng/L (NR 160–960 ng/L)
- Serum folate: 14.6 µg/L (NR 4.0–18.0 µg/L)
- Red cell folate: 86 µg/L (NR 160–640 µg/L).

Management

Whenever possible, treat with one haematinic only. In this patient, treat with hydroxocobalamin 1000 µg IM daily for 3 days.

Remember

Never give folate alone because, although it might partially correct the blood abnormalities associated with vitamin B₁₂ deficiency, it will also cause the B₁₂ level to drop even further and might precipitate severe neuropathy.

Do full blood counts + reticulocytes and urea and electrolytes initially daily (in a severely anaemic patient – as in this case) to look for:

- Hypokalaemia, which can occasionally develop 1–2 days post therapy
- Reticulocyte count, which starts to increase 2–3 days after treatment and reaches a peak on days 5–7
- The haemoglobin concentration, which often falls further before starting to rise
- Stay calm! Avoid blood transfusion. Failure of the reticulocyte count and haemoglobin to rise in the predicted manner might be due to:
 - Incorrect diagnosis and/or treatment: review laboratory data
 - Coexistent iron deficiency: check iron stores, e.g. ferritin levels
 - Intercurrent infection: review patient – chest infection? urinary tract infection?
 - Coexistent hypothyroidism.

Remember

Pernicious anaemia is an autoimmune disease; 1–2% of patients will also develop thyroid disease. Gastric cancer is also slightly more common (1–3% of cases).

The majority of patients with vitamin B₁₂ deficiency have vitamin B₁₂ malabsorption and require life-long treatment with vitamin B₁₂.

- **Treatment.** Hydroxocobalamin 1000 µg IM every 3 months is given but high doses of vitamin B₁₂ (2 mg) daily by mouth are also effective.

Nutritional deficiency of vitamin B₁₂ is rare and confined to vegans.

Further reading

Lahner E, Annibale B. Pernicious anaemia; new insights. *World J Gastro* 2009; **15**: 5121–5128.

Anaemia due to folic acid deficiency

These patients need 6 months' treatment with folic acid 5 mg daily after the cause (e.g. coeliac disease, see p. 51) has been defined and treated. Folic acid is, however, ineffective in the treatment of methotrexate toxicity, when folinic acid 15 mg IV daily is given.

HAEMOLYTIC ANAEMIA

Haemolytic anaemias are caused by increased destruction of red cells in two sites, intravascular or extravascular.

Case history

A 60-year-old woman presents with a history of feeling tired and exhausted for the last week. She is normally well but is under the care of the haematologists with chronic lymphatic leukaemia (CLL). She knows all about the condition, having been diagnosed

Continued

Case history (continued)

4 years ago. She is not on any treatment but is under regular follow-up.

On examination she is clinically jaundiced, with cervical lymphadenopathy and a just palpable spleen.

- Hb 68 g/L
- MCV 90 fL
- WBC $30 \times 10^9/L$
- Platelets $172 \times 10^9/L$
- Reticulocytes 18.8%
- Anisopoikilocytosis ++
- Polychromasia ++
- Spherocytes present
- Lymphocytosis with smear cells.

She has a normocytic anaemia with a raised white cell count and a reticulocytosis.

A normocytic anaemia can be due to:

- Acute blood loss
- Lack of erythropoietin – chronic kidney disease
- Bone marrow infiltration, e.g. carcinoma
- Haemolysis.

The patient described is anaemic and jaundiced with splenomegaly, suggesting a haemolytic anaemia. To confirm this you need to demonstrate:

- Increased red cell production
- A reduced red cell lifespan.

Increased red cell production

- Reticulocytosis: reticulocytes are immature red cells newly released from the bone marrow. They are larger than mature red cells, contain mRNA and appear polychromatic on standard blood films.
- Bone marrow aspiration: erythroid hyperplasia.

Remember

Cortisol, androgens and thyroxine are all required for optimal erythropoiesis.

Reduced red cell lifespan

- Acholuric jaundice: unconjugated hyperbilirubinaemia, urobilinogen but no bilirubin in the urine.
- Abnormal red cell morphology: this might also indicate the specific cause of the haemolytic anaemia (see below).
- Directly by radioactive isotope studies: reduced survival of ^{51}Cr -labelled autologous red cells (only performed if diagnosis of haemolysis is in doubt).

There are many specific causes of haemolysis. The diagnosis can often be made by review of the blood film. Speak to the haematology medical staff.

Features of haemolysis on blood film

- Spherocytes: autoimmune haemolytic anaemia, hereditary spherocytosis, *Clostridium welchii* septicæmia, extensive burns
- Red cell fragments: leaking mechanical heart valve, disseminated malignancy
- Sickled cells: sickle-cell anaemia, sickle-cell-HbC disease
- Bitten-out red cells: glucose-6-phosphate dehydrogenase deficiency, unstable haemoglobin, oxidative drug therapy, e.g. Dapsone
- Malaria parasites.

Investigations

- Antibody screen and direct anti-globulin test (DAT): in autoimmune haemolytic anaemia autoantibodies to red cell membrane antigens are present in serum and on the red cell surface
- Urinary haemosiderin: positive in chronic intravascular haemolysis such as paroxysmal nocturnal haemoglobinuria (PNH, very rare) and leaking mechanical heart valves
- Flow cytometry with antibodies against CD55 and CD59 antigens for PNH
- Glucose-6-phosphate dehydrogenase assay: common enzyme deficiency in particular ethnic groups (African, Mediterranean, SE Asian)

This patient had a strongly positive direct anti-globulin test (DAT) with anti-IgG (see Fig. 6.13, p. 129). The antibody eluted from her red cells was also present free in her serum and did not have any easily definable antigen specificity. She therefore has autoimmune haemolytic anaemia (AIHA) due to an IgG red cell autoantibody active at 37°C. AIHA can be primary or secondary. This patient is known to have CLL and has lymphadenopathy and a lymphocytosis with small, mature lymphocytes. Her AIHA is secondary to the underlying chronic lymphocytic leukaemia (CLL); 10–15% of patients with CLL develop AIHA.

- **Diagnosis.** Autoimmune haemolytic anaemia (secondary to underlying CLL).

Management

- Start oral prednisolone 60 mg/day. This usually produces a remission. Corticosteroids reduce the production of antibodies and also destroy antibody coated red cells.
- Blood transfusion is necessary if the haemoglobin continues to fall. Compatibility testing is complex because the autoantibody interferes with the cross-match; the laboratory could carry out autoabsorption studies to exclude additional alloantibodies. Transfuse slowly.
- Refer patient to her Consultant in Haematology to discuss further management.

Remember

AHA can develop acutely with a rapid fall in haemoglobin. This patient has a short history. Check the haemoglobin concentration at least once a day.

- **Progress.** This patient went into remission on the steroids. Steroids are effective in about 80% of cases. The haematologists gradually reduced her steroids over 3 months and she was started on azathioprine. A year later her CLL became active and she is now on rituximab and fludarabine.

SICKLE-CELL DISEASE

Case history

An 18-year-old female of African origin came to A&E with severe pains in her right leg, left hip, chest and back. She was well known to many of the staff as she had attended on many occasions with **painful sickle crises**. She had been out all night at a club.

The examination should initially be brief until adequate pain control has been achieved.

Investigations

Performed in medical assessment unit (MAU), aimed at assessing the severity of the crisis and determining any treatable cause:

- FBC + reticulocytes
- U&Es
- Liver biochemistry

Compare values with normal steady-state values, which should be in her notes. Remember that many nucleated red cells can result in an erroneously high WBC count:

- MSU
- Blood cultures

Infection is a frequent precipitant of a painful crisis:

- O₂ saturation on air (see Information box)
- Group and save

Questions to ask patients presenting with sickle-cell crises**Distribution of pain? Any bone tenderness?**

- Lumbar back pain can be particularly severe
- Rib, sternal or thoracic vertebral pain can impair respiratory effort and predispose to the acute chest syndrome.

Any precipitating factors?

- Exposure to cold/skin chilling (might apply to this patient)
- Dehydration (could also apply to this patient)
- Hypoxia
- Infection.

Information

A low O₂ saturation might reflect acute lung pathology, e.g. pneumonia or the acute chest syndrome, or chronic sickle-cell-related lung damage.

CXR and arterial gases are indicated only if there is:

- Rib, sternal and thoracic vertebral pain
- Signs of consolidation
- Tachypnoea (> 25/minute)
- O₂ saturation < 80% on air or < 95% on maximal supplementary O₂

Any fever?

- Fever ± leucocytosis can indicate an underlying infection but is also compatible with ischaemic tissue necrosis secondary to intravascular sickling alone.

Any hepatosplenomegaly?

- Splenomegaly is unusual in adults with HbSS or HbS/β⁰ thalassaemia – splenic atrophy is more common.
- A larger spleen than normal for the patient (ask the patient or parents/consult medical notes) might indicate acute splenic sequestration.

Compliance with hyposplenic prophylaxis?

- Patients with HbSS and HbS/β⁰ thalassaemia have severe hyposplenism and are susceptible to overwhelming sepsis, particularly with *Streptococcus pneumoniae*.
- Prophylaxis includes penicillin V 250 mg × 2 daily and vaccination with polyvalent pneumococcal and the Hib vaccines.

Treatment of acute painful sickle-cell crises**Analgesia**

- **Morphine/diamorphine**
- 0.1 mg/kg IV/SC every 20 minutes until pain controlled, then
- 0.05–0.1 mg/kg IV/SC (or oral morphine) every 2–4 hours
- Patient controlled analgesia (PCA) when pain controlled
- **NB** Ask patient about previous morphine dosages. Check medical records and discharge summaries. Higher doses may be required in cases who have previously received opioids.

Patient controlled analgesia (PCA) (example for adults > 50 kg)

- **Diamorphine**
- Continuous infusion: 0–10 mg/h
- PCA bolus dose: 2–10 mg
- Dose duration: 1 minute
- Lockout time: 20–30 minutes.

When using diamorphine or other parenteral opiates the following parameters must be monitored regularly on an hourly basis:

- Pain score
- Respiratory rate
- O₂ saturation on air
- Analgesia consumption.

Adjuvant oral analgesia

- Paracetamol 1 g 6-hourly
- +/- Ibuprofen* 400 mg 8-hourly
- or Diclofenac* 50 mg 8-hourly

Supplementary analgesia may be provided by:

- Regular oral dihydrocodeine and/or NSAIDs
- TENS
- Acupuncture
- Massage with analgesic rub
- Laxatives (all patients). For example:
 - Lactulose 10 mL × 2 daily
 - Senna 2–4 tablets daily
 - Sodium docusate 100 mg × 2 daily
 - Macrogol 1 sachet daily
- **Other adjuvants**
- Anti-pruritics:
 - Hydroxyzine 25 mg × 2 as required
- Antiemetics:
 - Prochlorperazine 5–10 mg × 3 as required
 - Cyclizine 50 mg × 3 as required
- Anxiolytic:
 - Haloperidol 1–3 mg oral IM × 2 as required.

*Advised with NSAIDs in renal impairment.

Remember

Failure to maintain oxygenation can:

- Exacerbate the painful crisis
- Indicate the development of the acute chest syndrome.

Hydroxycarbamide is useful in increasing HbF. It should be prescribed by haematologists and often takes months to have an effect. It reduces the episodes of pain, the acute chest syndrome and the need for blood transfusions. The overall mortality has also been shown to be reduced.

Supportive measures

- Keep warm: use heat pads
- Hydration: aim for 3 L per 24 h – orally if possible
- Venous access is often very difficult in these patients; to conserve peripheral veins the repeated insertion of IV lines should be avoided
- IV hydration is indicated if:
 - Nausea/vomiting is uncontrolled
 - The patient is sedated
 - The serum urea/creatinine are rising

- Oxygenation: aim for O₂ saturation 95%
- Monitor the haemoglobin concentration daily and transfuse if it falls to 150 g/L. All transfused blood should be matched for minor blood group antigens Kell and Rh (C and e, as well as D antigens). Remember, do not use transfusions in this steady-state anaemia, in an uncomplicated painful episode and for minor surgery.

The acute chest syndrome

Most painful sickle-cell crises resolve without complications within 7–10 days. The development of the acute chest syndrome is the most common cause of death in adults with sickle-cell disease.

The syndrome is characterised by:

- Rib, sternal and/or thoracic vertebral pain
- Bilateral basal chest signs with new infiltrates on CXR
- Tachypnoea
- Deteriorating oxygenation
- Falling haemoglobin concentration
- Fever and leucocytosis.

Pathophysiology of acute chest syndrome

- Infection
- Fat embolism from necrotic bone marrow
- Pulmonary infarction due to sequestration of sickled red cells.

Treatment of acute chest syndrome

- Exchange blood transfusion to reduce the amount of HbS to < 20%
- Maintenance of oxygenation: this might include, for example, continuous positive airway pressure (CPAP) via a tight-fitting mask, or intermittent positive pressure ventilation (IPPV)
- Aggressive pain relief
- Intravenous antibiotic therapy.

The majority of patients with a sickle-cell crisis present with severe, acute bone pain secondary to ischaemic bone marrow necrosis. Beware the patient with sickle-cell disease (SCD) who presents unwell but without pain. Such patients might have other, less common, complications of SCD, which can progress very rapidly (Figs 6.3 and 6.4).

Remember

Other complications of SCD include:

- Pneumococcal septicaemia
- Splenic sequestration
- Erythrovirus infection associated with marrow aplasia
- Acute folate deficiency

- **Progress.** This patient's current crisis was more severe than her previous ones and she went on to develop the acute chest syndrome from which she died.

TYPES OF SICKLE-CELL DISEASE

- Sickle-cell anaemia HbSS
- Sickle-cell-haemoglobin C disease HbSC

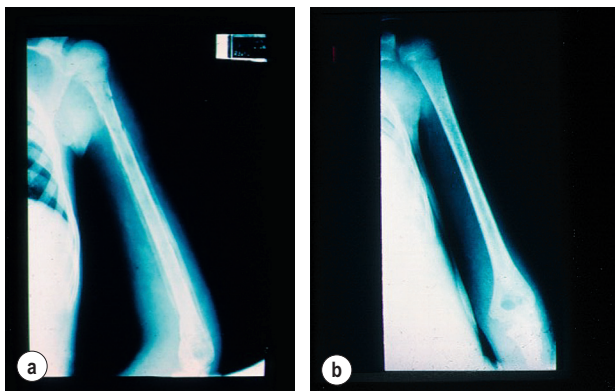


Figure 6.3 (a) Osteomyelitis of the humerus in a sickle patient (pre-treatment). Note the elevation of the periosteum at the distal part of the humerus. (b) The same patient showing normal periosteum following treatment.



Figure 6.4 Avascular necrosis of the femoral head in a patient with homozygous sickle-cell disease. There is loss of joint space and distortion of the head of the femur and acetabulum.

- Sickle-cell beta thalassaemia
- Rare compound heterozygotes, e.g. HbSD.

Diagnosis in A&E/MAU

- Information from patient
- UK Haemoglobinopathy card
- Blood count, reticulocyte count and blood film review
- Serum bilirubin
- Sickle solubility test (commercial kits are available).

Later:

- Haemoglobin electrophoresis (Fig. 6.5) on cellulose acetate membrane (CAM) at an alkaline pH

or

- High-performance liquid chromatography (HPLC).

Typically, the patient will be anaemic with evidence of haemolysis (elevated bilirubin and reticulocyte count). The blood film will show sickled red cells in variable numbers (Fig. 6.6). The sickle solubility test will be positive and CAM electrophoresis or HPLC will confirm the presence of HbS ± HbC or HbD with no HbA (except in HbS/ β^+ thalassaemia).

Beware

- In HbSC and HbS/ β^+ thalassaemia the haemoglobin concentration, reticulocyte count and serum bilirubin can be virtually normal.
- The sickle solubility test is a qualitative test only and will be positive in any individual where the amount of HbS is > 10%. This will include both sickle-cell trait and sickle-cell disease.

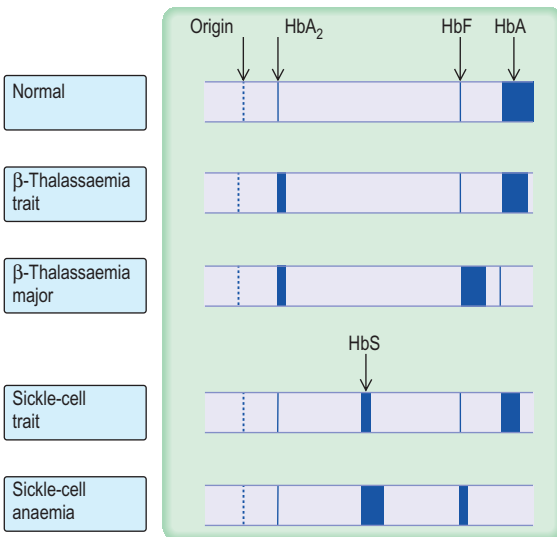


Figure 6.5 Patterns of haemoglobin electrophoresis.



Figure 6.6 Blood film in sickle-cell disease showing numerous sickle-shaped red cells.

Further reading

Rees DC, Williams TN, Gladwin MT. Sickle cell disease. *Lancet* 2010; **376**: 2018–2031.

ELEVATED HAEMOGLOBIN (POLYCYTHAEMIA)

Case history (1)

On your medical take you admitted a 70-year-old man with breathlessness, wheeze, fever and cough productive of sputum. As a long-standing smoker he suffers bouts of bronchitis but is otherwise in reasonable health.

On examination he was not breathless at rest. Pulse was 82/min with no evidence of cardiac failure. Auscultation of the chest showed scattered wheeze and a few crackles at both bases. Peak flow was 350 L/min.

Initial investigations have shown Hb 230 g/L, PCV 0.62, WCC $12 \times 10^9/L$, a mild neutrophilia and platelets $200 \times 10^9/L$.

Case history (2)

In the next bed a 54-year-old man has been admitted with chest pain and a suspected myocardial infarct. His general health is reasonable but he has developed severe night sweats and has lost 7 kg over the last 3 months. He denies smoking cigarettes and does not have any previous history of chest problems.

Case history (2) (continued)

On examination he looked well. Pulse and blood pressure were normal. There were no abnormal signs in the cardiac or respiratory systems.

Investigations show his Hb was 220 g/L with PCV 0.58, WBC $20 \times 10^9/L$ and platelets $600 \times 10^9/L$. Lactic dehydrogenase 740 U/L.

These two cases both have elevated Hb, but is their cause the same?

Haemoglobin (in red blood cells) is required for oxygen transport and, like most things, too much Hb has serious consequences and needs appropriate management (Fig. 6.7).

How to visualise the Hb level:

- Hb is expressed as a concentration, i.e. g/dL blood but blood = plasma + solids (RBCs mainly). Thus Hb level must be related to the level of the plasma.

Preliminary management

- Ensure no hyperviscosity symptoms or signs:
 - Confusion
 - Visual disturbance
 - Peripheral circulatory disturbance.

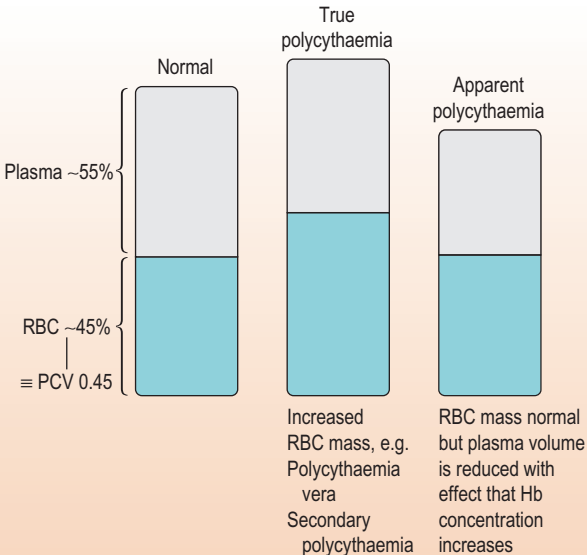


Figure 6.7 Alteration of haemoglobin in relation to plasma.

- Ensure patient is adequately hydrated.
- Infection (if present) must be treated.
- Identify correctable causes, e.g. chronic hypoxia.

Having made sure that the patients are stable, the next step is to determine the cause of the high Hb concentration. Before carrying out extensive investigation, it is sensible to contact the haematology team, who will either advise on further tests or take over the patient's care.

Information

Hb might be high in:

- Primary proliferative polycythaemia (polycythaemia vera, PV)
- Secondary to underlying hypoxic state: raised Hb serves a purpose:
 - Chronic lung disease
 - Cyanotic heart disease
- Inappropriately high level of erythropoietin production: raised Hb serves no purpose:
 - Renal cell carcinoma
 - Uterine tumours
 - Cerebellar haemangioblastoma
- Relative/apparent polycythaemia:
 - Where the plasma component is reduced with effect that Hb concentration rises, e.g. dehydration, associated with obesity, hypertension, diuretics, smoking

The haematology registrar advises you to arrange some investigative tests.

Investigations

- Repeat FBC (to check the result is correct or that with some oral/IV fluid the Hb has normalised). High haematocrit.
- Biochemistry screen: renal function – is it normal? Uric acid – might be high in some types of polycythaemia.
- Blood film: these patients had elevated platelets and WBC – make sure these are normal peripheral blood cells, with no evidence of leukaemia.
- Presence of JAK 2 mutation (see Remember box).
- Bone marrow (see Remember box).
- Erythropoietin levels (normal or low in PV).

Remember

Proposed criteria for PV

Modified from proposed revised WHO criteria for polycythaemia vera (PV).

Major criteria

- Haemoglobin > 185 g/L in men, 165 g/L in women or other evidence of increased red cells volume.

Remember (continued)

- Presence of JAK2 tyrosine kinase 617VF or other functionally similar mutation such as JAK2 exon 12 mutation.

Minor criteria

- Bone marrow biopsy, showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation.
- Serum erythropoietin level below the reference range for normal.
- Endogenous erythroid colony (EEC) formation in vitro*.

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria.

*EEC. This is not routinely available but colony formation in the absence of exogenous erythropoietin in vitro is 100% specific and sensitive in patients without previous treatment.

From: Tefferi et al. Blood (2007) 110:1092. American Society of Haematology.

For diagnosis of secondary cases

- Blood gases or pulse oximetry (the latter is painless and quite adequate to exclude hypoxia only).
- CXR: emphysema, other lung pathologies.
- Abdominal ultrasound: is the spleen enlarged? Remember renal and uterine causes of polycythaemia.
- Bone marrow: not diagnostic in isolation but gives additional information.
- Erythropoietin levels raised.

NB It is now not necessary to do blood viscosity and red cell volume studies.

Classic features of polycythaemia vera (PV)

- Weight loss, sweats, pruritus (itching is typically much more pronounced after a warm bath) (Fig. 6.8).
- High Hb and perhaps raised WBC + platelets.
- Splenomegaly ± hepatomegaly.
- Other causes (e.g. hypoxia) excluded.
- Increased red cell mass.
- Plasma volume normal.

Secondary polycythaemia

- As above, but generally with no hepatosplenomegaly, no thrombocytosis.
- Usually secondary cause found, such as cyanotic heart disease, lung disease, renal disease.

Apparent (or relative) polycythaemia

- Red cell mass normal
- Reduced plasma volume
- No hepatosplenomegaly.



Figure 6.8 Erythromelalgia of the toes (this is a painful complication in which the skin becomes suffused and red, as in this patient).

Management and progress

This is where knowledge of the underlying cause becomes crucial.

Your FIRST patient has secondary polycythaemia due to lung disease

This is a physiological rise in Hb. Reducing the Hb to normal could have serious consequences because the rise in Hb is a compensatory mechanism.

The initial aim is to reduce the Hb to a safe level. Generally this is achieved by venesection (removal of ~400–500 mL blood) every 2 days. In males the PCV is reduced to < 0.5 and in females to < 0.45.

ALL cases of secondary polycythaemia should be treated with venesection and treatment of the underlying cause if possible. This patient's raised Hb was due to chronic lung disease, with the high Hb due to hypoxia.

Your SECOND patient has polycythaemia vera (Remember box)

- Venesect 400–500 mL weekly.
- Then control marrow activity with hydroxycarbamide.
- Targeted therapy with JAK1 and JAK2 agonists is becoming available.

Long-term complications

Up to 30% of patients with PV will develop intense marrow fibrosis and 5% develop acute myeloid leukaemia. The other polycythaemias do not transform.

ELEVATED WHITE BLOOD CELL COUNT

Case history

A 17-year-old boy who has ulcerative colitis was admitted to MAU because he felt unwell with a headache, sore throat and a temperature. He had also developed diarrhoea but there was no blood in the stools. He was not on steroids but was on azathioprine 100 mg daily.

On examination his tonsils were enlarged and inflamed; he had palatal petechiae and cervical lymphadenopathy.

Investigations showed an Hb of 124 g/L, an MCV of 98 fL, WBC of $16 \times 10^9/L$ with abnormal lymphocytes in the peripheral blood. A monospot test is positive.

Diagnosis: Infectious mononucleosis.

There are many causes of a raised WBC (Table 6.1) and there is overlap with haematological malignancies, many of which present with WBC elevation. As a non-specialist confronted with a patient who has an elevated WBC, the key question is: does this elevation represent a haematological malignancy or is it reflecting some other process?

A thorough history and examination will usually allow you to determine the cause of the elevated WBC. 'Alert' features suggesting a possible malignant cause include:

- Ill patients
- Those with bleeding/bruising
- Fever
- Enlargement of liver or spleen or lymphadenopathy
- Weight loss
- Lymphocytes or bizarre/abnormal cells on blood film.

Is it glandular fever or acute leukaemia?

The atypical lymphocytes seen in this patient with an infectious mononucleosis can be confused with leukaemic blasts because the lymphocytes are large, often have nucleoli and resemble lymphoblasts. Specific tests, such

Table 6.1 Causes of high white blood cell counts

Patients with haematological malignancies likely to have high WBC	Situations in which a reactive high WBC occurs
Acute myeloid leukaemia	Infection
Acute lymphoblastic leukaemia	Corticosteroid therapy
Chronic lymphocytic leukaemia	Brisk GI tract bleeding
Chronic myeloid leukaemia	'Stress', e.g. postoperative
Lymphoma	Post splenectomy
Other infiltrations: myeloma, myelofibrosis	

as the 'Monospot', help confirm the diagnosis. In general, the haematology department will advise on further investigation, e.g. cell marker analysis to exclude leukaemia.

- **Progress.** This patient quickly improved, with no significant flare up of his colitis. He was sent home after 72 hours, continuing on azathioprine.

Remember

If in doubt – contact the haematology staff. Early intervention in a patient with acute leukaemia is advised and if you are not confident that the WBC rise is 'benign' – seek expert help. There is less urgency if:

- The patient is obviously well
- Isolated WBC only (Hb/platelets normal)
- Obvious infection
- Simple neutrophilia.

Further reading

Stock W, Hoffman R. White blood cells 1: non-malignant disorders. *Lancet* 2000; 355: 1351–1357.

ELEVATED PLATELET COUNT

Case history

A 75-year-old woman was admitted with acute ischaemia of the toes in both feet. On examination she was found to have dusky skin on both feet, with evidence of early gangrene in the toes. FBC showed normal Hb, WBC of $18 \times 10^9/L$ (neutrophilia) and platelet count $1500 \times 10^9/L$.

Other significant features in this patient:

- Evidence of weight loss
- Splenomegaly 4 cm below the costal margin.

You need to decide whether the marked elevation of the platelet count is likely to be *reactive* to some underlying process/disorder, or whether she has a *primary* marrow disorder, because the management is dictated by the underlying cause.

Why does the platelet count rise in a reactive manner?

In simplistic terms, any acute stress (bleeding, operative surgery, severe infection) causes intense marrow activity with elevation of white cells and platelets in a non-specific way.

Reactive thrombocytosis does not usually exceed $1000 \times 10^9/L$, whereas primary thrombocytosis is often $> 1000 \times 10^9/L$, but do not rely on platelet count alone. A reactive thrombocythaemia will resolve when the underlying problem, e.g. infection, is treated.

Immediate action

- Contact haematologist.
- Check end organs – are they threatened:
 - Look at fundi: vascular occlusion?
 - Extremities: too late at this point because there is vascular damage to feet in this patient
 - Renal function.
- Is there a secondary (reactive) cause:
 - Infection
 - Bleeding
 - Malignancy (breast, lung, bowel)
 - Connective tissue disorder (e.g. rheumatoid).

If none obvious – check again for splenomegaly, as was found in this case.

If platelets are raised + splenomegaly, then the cause is likely to be a myeloproliferative disorder.

- **Diagnosis.** This patient has a **myeloproliferative disorder**.

Is there a test that will confirm a primary bone marrow pathology?

Unfortunately not. The JAK2 tyrosine kinase mutation is only present in 50% of cases (see polycythaemia vera). Bone marrow trephine biopsy can help because increases in the numbers of megakaryocytes (the cells that make platelets; Fig. 6.9) with clustering favour a diagnosis of essential thrombocythaemia (ET), but often it is a diagnosis of exclusion. Blood film examination may show marked variation in size and shape of the platelets (platelet anisocytosis; Fig. 6.10) in primary thrombocythaemia – but this is not diagnostic.

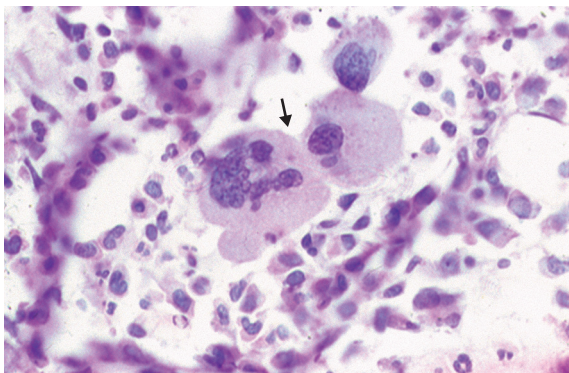


Figure 6.9 Bone marrow in essential thrombocythaemia: clusters of megakaryocytes (from which platelets bud off) are seen in the centre of the field.

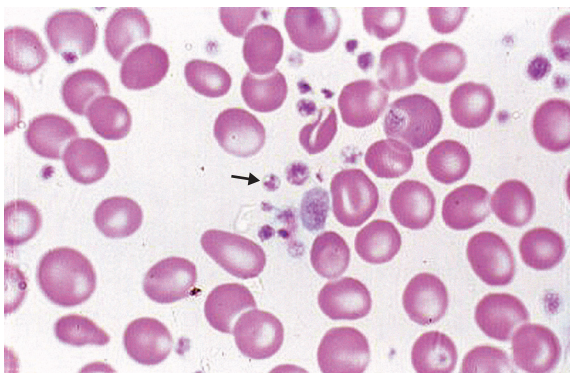


Figure 6.10 Large numbers of platelets (small purple cells) in blood film of patient with essential thrombocythaemia.

Information

Myeloproliferative disorders associated with thrombocytosis

- Primary (essential) thrombocythaemia
- Polycythaemia vera
- Chronic myeloid leukaemia
- Myelofibrosis

Management

- Give low-dose aspirin 75–300 mg/day (or dipyridamole if aspirin contraindicated).
- Plateletpheresis (using cell separator) if organ function threatened and need rapid reduction in platelet count.
- Oral hydroxycarbamide (e.g. 2–3 g per day for 2–3 days, dropping thereafter to 500 mg/day) to suppress bone marrow production of platelets (but beware neutropenia if dose too high). Suggested regimen: 10–30 mg/kg/day. Anagrelide and Busulfan are also used.

Complications

- Primary thrombocythaemia: generally indolent course but might transform to polycythaemia myelofibrosis in ~5% (occasionally transforms to acute myeloid leukaemia).
 - *Progress.* This patient was referred to the Vascular Surgical Department who carried out Doppler and Duplex imaging of his peripheral arteries but found no lesion amenable to surgery.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Definition

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in the hexose-monophosphate pathway. It is responsible for generating NADPH. In the

red cell, NADPH is a major source of reducing the potential required to maintain the iron atoms of haemoglobin in the ferrous state and to prevent membrane lipid peroxidation.

Case history

A 30-year-old Nigerian man was brought to A&E having collapsed in the street. He had returned from a 3-month holiday in Nigeria 6 days previously. Two days before admission he had developed central colicky abdominal pain and diarrhoea; 1 day before admission he began to feel weak and noticed his urine was discoloured red.

On examination he was pyrexial (37.8°C), anaemic and jaundiced. There was no hepatosplenomegaly.

Dipstix testing of urine was negative for bilirubin but positive for urobilinogen and blood. Urine microscopy revealed no red cells.

Investigations

- Hb 54 g/L
- MCV 91 fL
- WBC $15.8 \times 10^9/L$
- Platelets $249 \times 10^9/L$
- Reticulocytes 11.61%

Blood film showed polychromasia, irregularly contracted and bitten-out red cells. There were no malaria parasites or Heinz bodies.

The patient has a normocytic anaemia with a reticulocytosis suggesting **acute haemolysis or haemorrhage**.

Polychromasia refers to the appearance of reticulocytes, or immature red cells, when stained by using standard stains.

The appearance of the red cells is compatible with oxidative red cell damage. It is unusual to see Heinz bodies when patients have a functional spleen.

Differential diagnosis (see Table 6.4)

Malaria is a common cause of haemolysis in patients returning from the tropics. Other evidence to suggest acute intravascular haemolysis is shown in Table 6.2.

Hb electrophoresis on cellulose acetate membrane (CAM) and agar gel demonstrates sickle-cell trait but no other structural haemoglobin variant. Sickle-cell trait does not result in a haemolytic anaemia.

The negative isopropanol stability test excludes an inherited, unstable haemoglobin variant.

The negative DAT (or Coombs' test) excludes immune-mediated red cell destruction.

G6PD was assayed by two methods that confirmed G6PD deficiency. The most common G6PD variant in individuals of African descent is G6PD A⁻.

Table 6.2 Evidence to show intravascular haemolysis

Test	Result
Serum bilirubin	65 mmol/L
Serum haptoglobins	Undetectable
Serum LDH	587 iu/L
Schumm's test	Positive

Remember

- G6PD deficiency will be present in all (homozygous) males who carry an affected X chromosome
- Heterozygous females will have a dual population of red cells
- Because X chromosome inactivation is random (lyonisation), some heterozygous females will demonstrate clinical G6PD deficiency.

Deficiency of G6PD arises from a large number of different mutations in the G6PD gene, the majority of which are point mutations resulting in single amino acid substitutions. G6PD deficiency is widespread in many tropical and subtropical populations where malaria was, or is, endemic. Frequencies of 20% of the population in Southern Europe and Africa and 40% in south east Asia and the Middle East have been reported.

G6PD deficiency can present as:

- Neonatal jaundice
- Chronic haemolytic anaemia
- Acute haemolytic anaemia.

An acute haemolytic crisis is the most common presentation and most affected individuals are asymptomatic until this happens. Acute haemolysis occurs when an exogenous factor imposes an extra oxidative stress, which overwhelms the limited supply of NADPH in the red cells. Acute haemolysis can be precipitated by:

- Infection
- Drugs
- Fava beans (either lightly cooked food or as a pollen).

Many drugs (Table 6.3) have been implicated in attacks of acute haemolysis in susceptible individuals.

Remember

- Some drugs (e.g. primaquine, aspirin and vitamin K) can be given safely in reduced doses
- Some agents (e.g. Dapsone and naphthalene) in sufficient amounts will cause haemolysis in individuals with normal levels of G6PD.

Table 6.3 Drugs that commonly cause acute haemolysis in patients with G6PD

Type	Example
Anti-malarials	Primaquine Pamaquine Chloroquine Quinine
Sulfonamides	Sulfasalazine Dapsone Co-trimoxazole
Other antibiotics	Nitrofurantoin Nalidixic acid Quinolones, e.g. ciprofloxacin
Analgesics	Aspirin (> 1 g per day)
Miscellaneous	Vitamin K analogues Naphthalene Probenecid Dimercaprol Methylene blue

Favism is a form of severe, acute, intravascular haemolysis, often with massive haemoglobinuria, precipitated by exposure to fava beans (*Vicia faba*) in individuals with G6PD deficiency. It is most common in children, following the ingestion of fresh, raw beans. Haemolysis is probably precipitated by divicine, a glucoside constituent in fava beans, which generates free oxygen radicals when oxidised.

Diagnosis of G6PD deficiency

Clinical features

- Sudden onset
- Severe malaise and pallor often with fever and abdominal pain
- Dark urine
- Jaundice.

Remember

- The jaundice of haemolysis is prehepatic and the bilirubin is unconjugated and therefore does not appear in the urine
- The dark urine is partly due to haemoglobinuria and partly to increased urobilinogen which oxidises and darkens on standing.

Laboratory features

Blood count:

- Normocytic anaemia
- Reticulocytosis
- Bitten-out and irregularly contracted red cells.

The spleen 'bites out' Heinz bodies, which are aggregates of oxidised methaemoglobin, from affected red cells.

Features of intravascular haemolysis

- Decreased haptoglobins
- Increased LDH
- Haemoglobinaemia
- Haemoglobinuria
- Positive Schumm's test due to methaemalbumin.

One of the isoenzymes of lactate dehydrogenase (LDH) is found in high concentrations in red cells and is released in red cell damage.

Rapid depletion of haptoglobin with the formation of methaemalbumin is typical of intravascular haemolysis. In the absence of other scavenging serum proteins excess haem binds to albumin and the ferrous iron is subsequently oxidised to ferric iron to give methaemalbumin and a positive Schumm's test. The cause of the intravascular haemolysis was established by further tests, as shown in Table 6.4.

Haemoglobinuria might result in acute kidney injury, particularly in adults – monitor urine output, urea and creatinine.

Remember

- Old red cells have less G6PD than young red cells and are destroyed first during a haemolytic attack
- Newly formed reticulocytes have relatively high concentrations of G6PD
- As a result of these two factors the concentration of G6PD in an affected individual may rise during an acute haemolytic episode to within the normal range
- If in doubt retest 1 month later.

Assessment of G6PD activity

- Qualitative screening test, e.g. cresyl blue decolorisation test
- Quantitative enzyme assay by spectrophotometry.

Treatment

- Stop any drug that could have precipitated the acute haemolysis
- Search for and treat any infection
- Monitor haemoglobin concentration twice daily until stable
- Bed rest; urgent blood transfusion may be required in severe cases.

Table 6.4 Test results confirming the cause of intravascular haemolysis

Test	Result
Haemoglobin electrophoresis	HbA + HbS
Direct antiglobulin test (DAT)	negative
Isopropanol stability test	negative
G6PD assay	1.9 IU/gHb

- Patient education:
 - Issue G6PD deficiency card and information leaflet
 - Discuss avoidance of specific drugs and fava beans
 - Offer family screening.

What had precipitated a haemolytic crisis in this man with G6PD deficiency?

This was initially obscure. He denied any drug ingestion but, on repeated questioning, admitted drinking approximately 50 mL of an oily liquid he had obtained from his church in Nigeria where it was used for anointing the faithful. When he produced the bottle it smelt strongly of mothballs and ultraviolet spectrophotometry confirmed the presence of naphthalene. Naphthalene is well known to cause acute haemolysis. It was first described in the 19th century after the introduction of beta-naphthol to treat hookworm infestations. Many cases of affected infants have been described where the naphthalene was used as a moth repellent in clothes. The presence of G6PD deficiency greatly increases sensitivity to the oxidative red cell damage mediated by naphthalene.

- **Progress.** The patient's haemoglobin concentration did not fall any further but rose slowly, reaching 92 g/L 7 days later. The reticulocyte count peaked at 17.4% on the fifth day, and the jaundice had resolved by 14 days. Re-assay 6 weeks later confirmed G6PD deficiency.

BLEEDING DISORDERS

These can be due to inherited or acquired causes. Disorders are due to haemolysis (either intra or extra-vascular) or coagulation disorders. Always take a good history and use your common sense, as illustrated in the case below.

Case history (1)

You are phoned by a surgical specialist registrar asking for your advice. He has just finished a bilateral hernia repair on a 50-year-old man and the right side is bleeding briskly. The patient has required a transfusion with two units of blood in the last 30 min. The surgeon tells you that the surgery has gone well and wants you to sort out his clotting.

What do you think about this case?

This patient is most likely to be **bleeding from a surgical cause**: 2 units in 30 min is far in excess of what you would expect to give in a patient with a clotting disorder, and he is only bleeding from one of the repair sites, not both. Best to advise the registrar to find the bleeding vessel!

Although this might seem like a somewhat silly example, it shows that not all bleeding is due to abnormal clotting. Look at the whole picture before jumping in with fresh frozen plasma (FFP).

Inherited bleeding disorders

You are far more likely to see acquired bleeding disorders than inherited. Inherited disorders are uncommon, but must be identified.

Remember

Management of inherited disorders is complex: always seek specialist support.

How can I identify the inherited disorders?

Most inherited disorders of any severity present in childhood and hence most, if not all, patients will be able to tell you about their problem. They should carry a medical card with them, identifying the problem and their haematology consultant. It should be easy to sort out these patients and get in touch with the appropriate specialist. Always take any suggestion of an inherited bleeding disorder seriously (see Figs 6.11 and 6.12).

How can I identify milder forms?

Milder inherited disorders might not present until later in life and usually do so after surgery or other interventions.

Acquired bleeding disorders

As mentioned, these are far more common than inherited problems and are usually seen in particular clinical settings. These common scenarios will be outlined later. Most acquired disorders involve multiple and complex defects of coagulation.

Investigation of a suspected bleeding disorder

Should I check the clotting on everyone who bleeds?

Probably, although this isn't absolutely necessary; however, it is best to have a low threshold. A normal set of results might help you be more secure that you aren't overlooking something. Remember, however, always to take a full history and family history to try to identify any underlying inherited coagulation defect. For example, if a patient had:



Figure 6.11 Gross arthritis in a patient with haemophilia (inherited factor VIII or IX deficiency).



Figure 6.12 This patient with haemophilia A has bled into his foot (note the discoloration of the foot below the medial malleolus).

- Excessive bleeding after a previous haemostatic challenge:
 - Operation
 - Dental extraction
 - Trauma.
- Needed a previous blood transfusion for bleeding
- Family history of bleeding
- Epistaxis, easy bruising.

What should I request?

You request a basic coagulation screen:

- Full blood count to check platelet count
- Prothrombin time (PT)
- Activated partial thromboplastin time (APTT).

Remember

Even a 2-second prolongation might indicate an inherited clotting problem of significance and should be investigated more fully.

These are the minimum number of tests to start with. If you really want to check that a clotting disorder exists, then the following should also be performed:

- Fibrinogen level
- Thrombin time (TT).

These tests form your baseline investigations or screening tests.

Acquired disorders are relatively easy because clotting times are usually notably prolonged.

There are a whole range of specialist investigations for the complete study of a coagulation disorder: it is best to seek specialist advice.

Case history (2)

You are called to see a patient in A&E who is bleeding excessively from a dental extraction. The doctor in A&E thinks that the patient has liver disease and asks you for some help. There is nothing in the history to indicate what the liver problem might be and the patient denies excess alcohol consumption.

On examination you notice spider naevi, liver palms and splenomegaly. You agree that the excess bleeding is probably due to liver disease.

Bleeding in liver disease

This causes widespread coagulation and bleeding problems. Always be aware that significant liver dysfunction can result in a potentially severe bleeding disorder. The components of liver-related bleeding are:

- Reduced synthesis of coagulation factors: the liver is the source of all coagulation factors (apart from Factor VIII).
- Associated vitamin K deficiency: coagulation proteins might be synthesised but will not be active because of vitamin K deficiency.
- Thrombocytopenia: frequently secondary to splenomegaly from portal hypertension.
- Chronic low-grade disseminated intravascular coagulation (DIC): see p. 112.
- Abnormal fibrinogen synthesis: in liver disease, excess sialic acid residues are added to fibrinogen and hence an acquired dysfibrinogenemia occurs.

The classic laboratory defects would be:

- PT prolonged due to decrease in factor II, V, VII or X
- APTT prolonged due to decrease in all factors
- TT prolonged due to abnormal fibrinogen
- Fibrinogen degradation products (FDPs) increased (due to failure to remove from circulation ± chronic DIC).

Information

Causes of vitamin K deficiency

- Biliary obstruction
- Oral anti-coagulants
- Liver disease
- Malabsorption states
- Inflammatory bowel diseases (with ileal resection)

Management

- Give 10 mg vitamin K daily IV for 3 days
- For acute bleeding give 10–20 mL/kg FFP to replace all coagulation proteins
- If the fibrinogen level is low or TT prolonged, give cryoprecipitate to supply fibrinogen.
 - **Progress.** This man's bleeding stopped with help from the dental surgeons. The patient has been referred to the Liver Clinic for investigation and management of his chronic liver disease.

Case history (3)

A 49-year-old man has been on treatment for hypertension for years. His renal function has gradually deteriorated despite reasonable control of his blood pressure (now 130/80), stopping smoking and taking statin therapy (his present cholesterol is 3.2 mmol/L).

His present GFR is 32 mL/min/1.73m². He has recently suffered from bruising around his upper arms and shins.

Diagnosis: Chronic kidney disease

Anyone with significantly impaired renal function can have an acquired bleeding disorder. The major cause is toxic metabolites impairing platelet function, as is the case in this patient.

- **Is the APTT or PT abnormal in renal disease?** No. As mentioned above, the major defect is an acquired platelet disorder. The clotting times are usually normal.
- **Should the bleeding time be measured regularly in patients with renal disease?** No, but remember that renal disease is a cause of an acquired bleeding disorder and if you are planning surgery on the patient they might have a bleeding problem.
- **What can we do in renal failure?** There are several approaches to treatment but sorting out the renal problem first is the best option. Dialysis will improve platelet function; this is why few stable dialysed/controlled patients actually bleed. The real risk group is those with a very high serum creatinine/urea.

Other treatments for bleeding include:

- Synthetic vasopressin analogue (desmopressin)
- Cryoprecipitate
- Platelet transfusion.

These are all used in bleeding episodes.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

This is the most complex of the acquired bleeding disorders.

DIC is inappropriate and continued activation of coagulation that leads ultimately to both bleeding and thrombosis.

The initial phase of DIC is thrombosis. This is why DIC is associated with end-organ damage leading to multi-organ failure.

Remember

DIC is always secondary to some other major clinical problem.

Bleeding arises as a secondary phenomenon due to consumption of coagulation factors and platelets (due to continued activation of clotting) and the activation of fibrinolysis (breaking down any fibrin that gets laid down).

Case history (4)

A 29-year-old man is brought to the Trauma Unit with severe injuries to his abdomen and legs as a result of a road traffic accident. Initial examination and CT scanning confirm that he has fractured both femurs and has a fractured pelvis. He has fluid in his abdomen on CT, suggesting internal organ damage.

He is resuscitated and taken to ITU where he needs ventilation, volume replacement and cardiovascular support with inotropes. His leg fractures are stabilised and he undergoes emergency laparotomy with resection of damaged small bowel. He initially improved but then his renal and liver function deteriorated and he was diagnosed as having multi-organ failure. He was then noted to be bleeding from his laparotomy wound.

- **Action**

- Always think about DIC in a bleeding patient
- Try to make the diagnosis.

- **Causes**

- Infection
- Obstetric complications
- Surgical
- Trauma
- Malignancy
- Liver disease
- Transfusion reactions.

If someone is bleeding and you always think about DIC you won't go wrong. In many ways the long list of causes is academic when you first see the patient – but if they have got DIC you must identify the cause.

- **How do I make the diagnosis?** Send off all the screening tests and fibrinogen degradation products (FDPs). The pattern is:
 - Platelets low: consumption
 - PT prolonged: consumption
 - APTT prolonged: consumption
 - TT prolonged: consumption of fibrinogen and FDPs
 - Fibrinogen low: consumption
 - FDPs high: breakdown of fibrin.
- **Why are FDPs measured?** FDPs tell you that fibrin is being broken down. The most specific test is the D-dimer, which tells you that cross-linked fibrinogen has formed and has then been broken down.

• How do I manage DIC?

- Treat the underlying disorder.
- Treat the underlying disorder!
- Treat the underlying disorder!!
- Support with FFP, cryoprecipitate and platelets.

Remember

People die from their underlying disorder rather than the DIC per se.

You must aim to treat the underlying disorder! DIC is always secondary. As mentioned earlier, it is due to inappropriate and continued activation of clotting. Until you stop this by treating the underlying problem it won't get better.

Blood component therapy is purely supportive. Give:

- 10–20 mL/kg FFP + cryoprecipitate
- Platelets
- Blood as required.

Aim to get the fibrinogen concentration to normal and the PT/APTT to within 4 s of normal.

- **Progress.** Despite all efforts the patient died.

Case history (5)

A 50-year-old patient has carcinoma of the lung with a prolonged PT, APTT, TT, low fibrinogen and platelet count and high FDPs, but he isn't bleeding.

Has this patient got DIC?

This is the picture of subclinical DIC – laboratory abnormalities but no bleeding. It is seen in chronic DIC, e.g. in liver disease, malignancy. DIC ranges from florid bleeding to abnormalities that are picked up only by laboratory testing.

Remember

People die from their underlying disorder rather than the DIC per se.

Anti-coagulant overdose

An obvious cause of bleeding. Don't forget to look for warfarin/heparin usage.

Action

Confirm anti-coagulant overdose by finding a prolonged PT (warfarin) or APTT (heparin). The treatment of bleeding depends on the problem, but in essence:

If due to warfarin: STOP WARFARIN

- Minor bleeding: If INR > 6.0: restart warfarin when INR < 5.0; check INR daily. If INR > 8.0 give vitamin K 2.5 mg oral or 0.5 mg IV.
- Major bleeding: give prothrombin complex concentrate 50 units/kg or FFP 15 mL/kg; give vitamin K 5 mg IV.

Remember

High prothrombin time (due to warfarin) without bleeding usually requires no treatment apart from stopping warfarin.

If due to heparin: STOP HEPARIN

If bleeding is excessive or uncontrolled:

- Protamine reversal (1 mg IV neutralises 100 units heparin – maximum dose 40 mg). Protamine has no effect on low molecular weight heparin.
- Seek advice.
- Heparin excess will correct in a few hours.

Remember

New thrombin inhibitors that are now being used for anti-anti-coagulation, e.g. dabigatran, apixaban and rivaroxaban have no antidotes.

Surgical cause

Suspect if rapid blood loss at operation. Don't underestimate the number of times this is forgotten and people chase a medical cause for bleeding when a vessel has a hole in it.

If you have a hole in a vessel bleeding won't stop until the hole is fixed, however good the coagulation system is.

Remember

Surgical and medical bleeding might coexist. If you correct the coagulation and the patient is still bleeding, think surgical whatever the surgeon says!

PLATELET DISORDERS**Case history (1)**

You are asked to see a 24-year-old woman who is in A&E. She has presented with petechiae scattered over her body. The casualty officer has found that she has a platelet count of $10 \times 10^9/L$. This woman seems very well and tells you that she has had

Case history (1) (continued)

the petechiae for at least a week. She has no other symptoms. She is on the contraceptive pill and is taking no other tablets. She does not smoke and drinks wine (6 units) at the weekend only.

On examination she has petechiae over her trunk, arms and legs. She has no other abnormal signs.

Investigations

You note the platelet count and also that all the other parameters in her blood count are normal. She also has normal routine biochemistry.

Remember

Meningococcal septicaemia has a purpuric rash and/or petechiae.

There are multiple causes of thrombocytopenia (Table 6.5). Thrombocytopenia may be the presentation of another disorder rather than a primary platelet disorder. All patients with severe thrombocytopenia (defined as $< 20 \times 10^9/L$, which produces spontaneous haemorrhage) require admission for investigation/treatment.

Remember

The list of causes (Table 6.5) is not comprehensive and excludes inherited thrombocytopenia or causes that would present in childhood.

Questions that need to be answered immediately

- Does this patient have immune thrombocytopenic purpura (ITP)?
- Does she have acute leukaemia?
- Does she have aplastic anaemia?
- ITP: normal Hb, normal WCC, no hepatosplenomegaly or lymphadenopathy.
- Acute leukaemia (see p. 132): high WCC, abnormal white cells on film, lymphadenopathy, hepatosplenomegaly (occasionally).
- Aplastic anaemia: low Hb, low WCC, no lymphadenopathy, no hepatosplenomegaly.

The **diagnosis appears to be ITP**. You are called back to see the patient 20 minutes later as she has had a massive haematemesis. You think the diagnosis is ITP as there are no other features to make you think it is aplastic anaemia or acute leukaemia.

Major bleeding in ITP is not common but can be a serious complication. Treatment approaches should be decided by a haematologist.

Table 6.5 Causes of thrombocytopenia

Failure of platelet production**Marrow aplasia****Metabolic defects**Vitamin B₁₂/folate deficiency

Uraemia

Alcohol excess

Liver disease

Drugs

Chemotherapy ± radiation

Marrow infiltration:

Leukaemia

Lymphoma

Myeloma

Myelofibrosis

Carcinoma

Decreased platelet survival**Immune:**

Immune thrombocytopenic purpura (ITP)

Systemic lupus erythematosus (SLE)

Chronic lymphatic leukaemia (CLL)

Hodgkin's lymphoma

Drug related

Infection

Malaria

Virus infection

Consumption:

DIC

Extracorporeal circulation

Haemolytic uraemic syndrome

Thrombotic thrombocytopenic purpura (TTP)

Loss from circulation:

Splenomegaly

Massive transfusion

Management for this patient

- Adequate and secure IV access
- ABO and Rh (D) group and cross-match 6 units of blood
- Fluid and blood replacement as appropriate
- Start high-dose IV immunoglobulin infusion 0.4 g/kg/24 h
- Platelet transfusion: 2 units immediately
- Oral prednisolone: 1 mg/kg daily.
 - **Progress.** She had no further haematemesis and her platelet count rose to $50 \times 10^9/L$ on Day 5 but remained at that level. After discussion she was referred for splenectomy, which produced a good response in her platelet count. See p. 124 for management of a splenectomised patient.

Learning points

- High-dose immunoglobulin elevates the platelet count by macrophage Fc receptor blockade of the reticuloendothelial system.
- Endogenous platelets usually rise after 24–48 h; the survival of exogenous platelets is improved.
- Platelet transfusion is usually not necessary in ITP except in the situation of life-threatening haemorrhage, such as in this case.
- 75% of patients respond to oral steroids but the full therapeutic effect may take 2–4 weeks to develop.

Remember

ITP might become chronic and might require long-term treatment ± splenectomy. Romiplostim and eltrombopag, thrombopoietin receptor agonists, are now being used if splenectomy has no effect.

Further reading

Provan D, Newland A. Fifty years of idiopathic thrombocytopenic purpura (ITP): management of refractory ITP in adults. *British Journal of Haematology* 2002; **118**: 933–944.

Imbach P, Crowther M. Thrombopoietin receptor agonists for primary immune thrombocytopenia. *N Engl J Med* 2011; **365**: 734–741.

Case history (2)

You are asked to see a 50-year-old man on a surgical ward who has come into hospital for an elective hernia repair. He is found on a routine preop FBC to have a platelet count of $90 \times 10^9/L$. His Hb and WCC count are normal.

This chronic presentation of mild thrombocytopenia is reasonably common. To establish the cause you should systematically go through the causes of thrombocytopenia from an initial clinical history and examination.

Can he go ahead and have his hernia repair?

It might take a while to get to the bottom of his thrombocytopenia. Elective surgery can be performed as the platelet count is greater than $80 \times 10^9/L$.

Avoid any NSAIDs as postop analgesia; make sure aspirin has not been taken within the last 10 days.

This man was discharged following a successful surgical repair and one week later his platelet count was $96 \times 10^9/L$. By 1 month the platelet count was normal. No clear reason for the thrombocytopenia was found but a **viral cause** seemed the most likely.

Case history (3)

A 28-year-old woman has had a D&C for long-standing menorrhagia. She is now 5 days after the procedure and still bleeding. She has been back in theatre and no local defect is found. She says she had problems in the past with bleeding after dental extractions. Her PT and APTT and platelet count are normal.

Diagnosis

This is the typical picture of an **inherited platelet disorder**. Severe platelet function disorders present in childhood but milder versions do not usually present until surgery in adulthood. Clues here are bleeding after dental extraction and long-standing menorrhagia.

Management

Assess the extent of bleeding. Treatment options include:

- Tranexamic acid 1 g × 4 daily if mild bleeding
- Platelet transfusion if severe bleeding.

In a classic platelet function disorder the bleeding time is prolonged, but this test is difficult to perform. If you suspect a platelet function disorder organise platelet function studies with your haematological laboratory.

- **Progress.** This patient stopped bleeding following a platelet transfusion. She was referred to the Haematology Department for follow-up.

THROMBOSIS

Case history (1)

You are asked to see a 24-year-old woman who has had a life-threatening pulmonary embolus. She received fibrolytic therapy (p. 286) on the ICU. Her condition stabilised and she is now on warfarin following initial treatment with low molecular weight heparin. She wants to know why she has had a pulmonary embolus. She has a family history of DVT.

Are investigations indicated?

Thrombosis is common but relatively uncommon under the age of 45 years unless there is a precipitating event (see below). In such patients with a family history, about 50% have a definable underlying prothrombotic state. It is well worth formally investigating her for a prothrombotic state.

Attempt to identify any precipitating event, such as:

- Taking combined oral contraceptive pill
- Immobility and/or recent surgery/fracture/injury
- Long-haul flight
- Obesity
- Malignancy.

Should she be investigated now or later?

She is on warfarin, which can interfere with thrombotic investigations. Identifying an underlying thrombotic state acutely will not change the immediate management.

Remember

- An abnormal result after an acute thrombosis does not mean an abnormality genuinely exists
- It must be rechecked
- However, a normal result is normal.

She is on warfarin so formal studies must be delayed. Refer her on to a specialist for follow-up and investigation.

What investigations will be requested after stopping warfarin?

Investigations

- Lupus anti-coagulant
- Anti-phospholipid antibody
- Protein C deficiency
- Protein S deficiency
- Anti-thrombin deficiency
- Factor V Leiden
- 3' prothrombin UTR variant
- JAK 2 mutation

These aim to look for an inherited deficiency of natural anti-coagulants, mutations leading to increased thrombin generation or acquired causes of a prothrombotic state.

- **Progress.** This woman has Factor Leiden deficiency. She is referred on to a specialist for long-term follow-up and counselling and family studies.

Case history (2)

You are asked to see a 70-year-old man who had a DVT after a knee replacement despite DVT prophylaxis. He has no family history of venous thrombosis. He is at present on warfarin following treatment with LMW heparin.

Should he be investigated for thrombophilia? No!

It is likely that at this age a DVT in this setting has been precipitated by the surgery. The pick-up rate for a significant thrombotic disorder is very

low in this setting. When asked to assess the thrombotic status, balance the likelihood of finding a defect against the value of identifying the exact defect.

Case history (3)

You are called to see a 45-year-old man who is being anti-coagulated for acute iliofemoral vein thrombosis with heparin. His APTT remains normal on 28 000 units heparin per 24 h. The dose of heparin has been progressively increased over the last 3 days but his leg swelling is worse.

What do you advise?

The target APTT for heparin for an acute thrombosis is 1.5–2.5 times the mid-point of the normal range. The most common reasons for failure are:

- Under-monitoring
- Underdosing
- Not actually receiving dose of heparin prescribed.

Action

- Ensure prescribed dose is being given.
- Increase dose by 10% per 24 h.
- Recheck APTT in 4 h.
- If still low, repeat the 10% increase in heparin dose and recheck at 4-hourly intervals.

Heparin monitoring is notoriously bad in most hospitals. If IV heparin is being used it should be monitored as follows:

- Check APTT every 4 h until target reached.
- Increase dose in 10% increments.
- Once target APTT reached, repeat at 4 h.
- If stable APTT, repeat 12-hourly.

Remember

- Outcome is dependent on the effectiveness of anti-coagulation within the first 48 h
- Heparin resistance is rare; poor heparin control is very common

For how long should a patient with venous thromboembolic disease be anti-coagulated with warfarin?

The duration and target INRs for various thrombotic conditions are listed in Table 6.6.

Recurrent VTE is essentially two or more events. The more events, the greater the likelihood of recurrence.

Long-term anti-coagulation carries the risk of major haemorrhage (4% per annum) and death (~0.5% per annum). These must be balanced against

Table 6.6 Duration and target INRs for thrombotic conditions

	Duration	INR target
Uncomplicated DVT	6 months	2.5
Complex DVT	6 months	2.5
Pulmonary embolus	6 months	2.5
Recurrent VTE	Indefinite	2.5 – if the recurrent event occurs whilst taking warfarin the intensity of anti-coagulation is increased, target 3.5
AF	Indefinite	2.5
Mechanical heart valves	Indefinite	3.5

AF, atrial fibrillation; DVT, deep vein thrombosis; INR, international normalised ratio; VTE venous thromboembolism

recurrence prevention. Complications are far more common in older patients.

Recurrence is much higher in patients anti-coagulated for 6 weeks rather than 6 months.

Remember

- Drug interactions with warfarin
- Need to amend dosage in patients undergoing invasive procedures
- Regular anti-coagulant clinic follow-up.

New orally active anti-coagulant drugs

A number of orally active direct thrombin and Xa inhibitor drugs (dabigatran, rivaroxaban) are being used in clinical trials for prevention and treatment of thrombosis. Such drugs have a much broader therapeutic window than warfarin and offer the prospect of fixed drug dosing without the need to monitor coagulation. They do not, however, have specific antidotes.

Case history (4)

You are asked to see a 36-year-old woman with an acutely swollen calf. Clinical diagnosis is a distal DVT. She has no complicating problems.

How should she be treated?

Initially, the diagnosis should be confirmed by venous compression ultrasonography (sensitivity 97% for proximal and 73% for calf veins). An acutely swollen leg has a range of causes:

- DVT
- Ruptured Baker's cyst
- Rupture of head of gastrocnemius
- Acute knee injury
- Haematoma
- Infection (e.g. cellulitis).

Action

If a DVT is confirmed:

- Give SC low molecular weight (LMW) heparin
- Warfarinise the patient.

This can be managed in outpatients with good nursing and laboratory support.

If the DVT is complex (i.e. iliofemoral):

- Admit
- IV unfractionated heparin or LMW heparin
- Warfarinise.

There is an increasing move to outpatient management of venous thromboembolism (VTE).

Dabigatran (see above) is being used instead of warfarin in some centres.

Case history (5)

You are phoned about a 36-year-old man with an acute right lower limb ischaemia due to an arterial thrombosis. He has a family history of thrombosis. There has been improvement in the ischaemic area over 24 hours. The patient is on intravenous heparin infusion and is being monitored by the vascular surgeons. The houseman wonders in view of the family history whether he should be investigated for thrombophilia. He has already sent off standard thrombophilia screen (see Investigations box, p. 118) and he asks if this is all that you need.

You tell him that thrombophilia is uncommon in arterial disease but there are a number of risk factors for arterial thrombosis. You suggest he requests:

- Plasma homocysteine
- Lipid profile
- Plasminogen activator inhibitor.
- Finding a cause in arterial disease is less likely than in venous thrombosis.

- **Progress.** No evidence of thrombophilia was found in this man but he is a smoker and his cholesterol was 7.4 mmol/L with risk factors for atherosclerosis. His lifestyle issues were addressed by the cardiac rehabilitation nurse specialist and he was started on a statin.

Case history (6)

You are asked to see a 60-year-old woman with a right leg DVT, who is on unfractionated heparin. She has been in hospital for 5 days and started warfarin therapy 48 hours previously. She has now developed a cold, painful leg on the left that is pulseless. You are told her platelet count has been falling since starting heparin.

What is the most likely diagnosis to consider?

This would be a good picture for **heparin-induced thrombocytopenia with thrombosis (HIT)** of the artery. The classic features are progressive platelet decline and new thrombosis. HIT is a clinical diagnosis and is diagnosed in any patient on heparin whose platelet count falls significantly.

Action

- Stop *all* heparin (including heparin flush).
- Contact haematologist.
- Alternative forms of anti-coagulation are not required for the DVT in this woman because she is on warfarin and the INR is 2.0 and heparin was about to be discontinued.

HIT is due to an immune induction of anti-heparin/PF4 antibodies which bind to and activate platelets via a Fc receptor. This results in a prothrombotic state with low platelets. There is usually a previous history of heparin exposure.

NB

- Fatal thrombosis, both venous and arterial, can arise if heparin is not stopped immediately.
- HIT can occur after SC heparin use. It is becoming increasingly common with the widespread use of heparin prophylaxis.
 - **Progress.** This woman has left acute ischaemic lower limb and required surgical removal of the thrombus in her popliteal artery. She fortunately made a good recovery although she still has a swollen, painful right leg (from the DVT) and ischaemic pain in the left leg after exertion.

SPLENOMEGALY, SPLENECTOMY AND HYOSPLENISM

Case history (1)

A 55-year-old man presented with a 3-month history of discomfort in the left side of his abdomen. The discomfort is present most of the time and now seems to be getting worse.

He has had rheumatoid arthritis for many years but his condition has stabilised on methotrexate therapy and occasional use of diclofenac for pain in his knees.

On examination he looks pale, he has evidence of rheumatoid arthritis in his hands with ulnar drift and palmar subluxation of the

Case history (1) (continued)

MCPs. He has rheumatoid nodules in both elbows. Both knees are deformed. Examination of his abdomen shows a large spleen.

Investigations show a normochromic normocytic anaemia with low platelets and a neutropenia.

The diagnosis is **Felty's syndrome** in a patient with rheumatoid arthritis.

Felty's syndrome consists of splenomegaly and neutropenia in a patient with rheumatoid arthritis. A normochromic, normocytic anaemia of chronic disease is usually seen, although iron deficient and rare haemolytic (Coombs' positive) anaemias are seen. Hypersplenism causing a pancytopenia may occur (see below).

Spleen size can be assessed by abdominal palpation or by imaging, e.g. ultrasound. CT, MRI and PET scans are also used to delineate the cause, e.g. lymphoproliferative disease.

There are many causes of splenomegaly, with the most frequent showing geographical variation. In temperate climates, malignant blood diseases, portal hypertension, haemolytic anaemias and infective endocarditis account for most cases, whereas in tropical countries malaria, leishmaniasis and the haemoglobinopathies are prevalent.

Information

Causes of splenomegaly

- Malignant haematological disease: e.g. acute or chronic leukaemia, malignant lymphoma
 - Myeloproliferative disorders: e.g. polycythaemia vera, myelofibrosis (often massive)
 - Haemoglobinopathies: e.g. β -thalassaemia major, haemoglobin, H, SC or E disease
 - Haemolytic anaemias: e.g. hereditary spherocytosis
 - Congestive splenomegaly: e.g. portal hypertension (cirrhosis)
 - Inborn errors of metabolism: e.g. Gaucher's disease
 - Auto-immune rheumatic disorders: e.g. SLE, rheumatoid arthritis (Felty's syndrome)
 - Infections:
 - Viral, e.g. infectious mononucleosis
 - Bacterial (any bacteria), occasionally – remember infective endocarditis
 - Protozoal, e.g. malaria, kala-azar
 - Miscellaneous (rare): e.g. amyloid, tropical splenomegaly.
- Enlargement of the spleen from any cause can be complicated by **hypersplenism**. This is characterised by:
- Splenomegaly
 - Pancytopenia
 - Normal or hypercellular bone marrow.

Pathophysiology of hypersplenism

Mature red cells, neutrophils and platelets 'pool', or are trapped, in the sinusoids of the large spleen and prematurely destroyed.

Hyposplenism may be due to:

- Congenital absence
- Splenectomy: surgical or by irradiation
- Splenic atrophy, e.g. coeliac disease, chronic inflammatory bowel disease
- Splenic infarction, e.g. sickle-cell anaemia (HbSS)
- Splenic infiltration.

Remember

Surgical splenectomy might be carried out because of:

- Trauma
- Treatment, e.g. hereditary spherocytosis, idiopathic thrombocytopenic purpura or myelofibrosis.

Splenic function can be assessed by:

- Peripheral blood film: look for abnormal red cells:
 - Acanthocytes = spiky red cells
 - Target cells = like an archery target
 - Pappenheimer bodies = iron granules
 - Howell–Jolly bodies = nuclear DNA fragments
- Differential interference microscopy of blood: increased pitted red cell (red cells with submembrane vacuoles) count
- Radioactive spleen scan (see above).

The functional size of the spleen can be assessed by scanning with a scintillation counter following the injection of radiolabelled (^{99m}Tc), heat-damaged, autologous red cells. These cells are removed from the circulation solely by the spleen.

- **Progress.** This patient with RA was confirmed as having Felty's syndrome as the cause of his splenomegaly. Over the following year he developed recurrent infections with a persistent, refractory neutropenia and eventually had a splenectomy.

Case history (2)

A 6-month-old baby boy of Nigerian parents was admitted to A&E, collapsed and unconscious. The family was travelling to the airport by taxi and diverted the car to hospital when the baby became suddenly unwell. Twelve hours before admission the child had been seen at a different A&E department with a short history of poor feeding, irritability and diarrhoea. He was noted to be febrile but not thought to be seriously unwell.

On examination the child was noted to be pale, with a GCS of 5. He was febrile at 39.5° with a firm spleen extending to below

Case history (2) (continued)

the umbilicus. Shortly afterwards, the child had a cardiorespiratory arrest and could not be resuscitated. The results of a blood count and blood film taken before death were:

Blood count	Blood film
Hb 24 g/L	Polychromasia
MCV 76 fL	Very reduced platelets
WBC $30.5 \times 10^9/L$	Nucleated red cells
Platelets $27 \times 10^9/L$	Occasional elongated sickle cells
Reticulocytes 7.0%	Diplococci both within neutrophils and macrophages and free in the plasma

Subsequent investigations demonstrated *Streptococcus pneumoniae* on blood culture.

- **Diagnosis.** Sickle-cell anaemia with pneumococcal sepsis.

Haemoglobin electrophoresis showed:

- HbS:90%
- HbF: 8%
- HbA₂: 1.8%.

Remember

Prevention of pneumococcal sepsis in babies with sickle-cell anaemia is dependent on maternal antenatal haemoglobinopathy.

At-risk pregnancies need to be identified and screened:

- Haemoglobinopathy screening of cord blood samples
- Institution of penicillin prophylaxis by 8 weeks of age.

- **Progress.** This baby presented moribund with splenomegaly, severe anaemia and thrombocytopenia. The reticulocytosis/polychromasia and nucleated red cells suggested a haemolytic anaemia. Haemoglobin electrophoresis subsequently confirmed sickle-cell anaemia (HbSS). The sickle-cell mutation affects the beta-globin gene and only assumes clinical importance 4 months after birth, when gamma-globin gene activity is suppressed and the beta-globin gene activated.

This child's death was due to overwhelming infection with *Streptococcus pneumoniae*, which was present in enormous numbers in the bloodstream. The thrombocytopenia was almost certainly related to DIC secondary to the bacterial infection. Severe hyposplenism is a characteristic feature of sickle-cell anaemia and is established by 4–6 months. Pneumococcal sepsis secondary to hyposplenism is a common cause of death in children less than 3 years old with sickle-cell anaemia.

The gross splenomegaly and severe anaemia were due to acute splenic sequestration of sickled red cells within the spleen, which often accompanies pneumococcal sepsis in this age group (see p. 126).

Overwhelming post-splenectomy infection (OPSI) is the most feared complication of hyposplenism.

Remember

- The greatest risk of OPSI following splenectomy is in the first 2 years but the increased risk is lifelong
- The mortality rate with OPSI due to *Streptococcus pneumoniae* is 50% despite treatment.

Pathophysiology

- Decreased antibody synthesis
- Decreased phagocytosis of opsonised bacteria.

The major pathogens involved in OPSI are:

- *Streptococcus pneumoniae* > 80%
- *Haemophilus influenzae* type B
- *Neisseria meningitidis*.

These are all encapsulated bacteria – the spleen is a vital first line of defence against encapsulated organisms. Severe infections in the hyposplenic patient can also occur in malaria and babesiosis (mosquito and tick bites, respectively) and following dog bites with *Capnocytophaga canimorsus*.

Remember

- Following vaccination check adequacy of antibody response
- Repeat antibody levels at 5 years post-vaccination and give booster doses if appropriate.

Prevention of OPSI depends on:

- Identification of the patient at risk
- Education of the patient about the risks of infection, dog bites and tropical travel
- Issue of a 'post-splenectomy' card and leaflet to the patient
- Lifelong prophylactic antibiotic therapy, e.g. penicillin V 250 mg × 2 daily
- Vaccination with a pneumococcal polysaccharide conjugate vaccine and the Hib vaccine.

BLOOD TRANSFUSION

The Blood Transfusion Department supplies red cells, platelets and plasma products, such as fresh frozen plasma, cryoprecipitate and human albumin.

The efficient and safe provision of blood products depends on good communication between you and the laboratory, and accurate patient identification.

Always

- Provide complete and accurate patient identification on the blood sample and request form.
- Tell the Blood Transfusion Department how much of what blood product is required and the urgency of the clinical situation.

Never

- Take blood from more than one patient at a time.
- Prelabel the blood sample tube.

Remember

When you request blood always make clear the urgency of the clinical situation:

- Very urgent: there is a life-threatening haemorrhage and blood is required in 1–5 min:
 - ACTION: No pre-transfusion compatibility test. The laboratory will issue group 0 Rh(D) negative blood
- Urgent: blood required in 5–10 min:
 - ACTION: ABO and Rh(D) group on patient sample. The laboratory will issue ABO and Rh(D) group compatible blood
- Non-urgent: blood required in 30–60 min:
 - ACTION: Full pre-transfusion compatibility test. The laboratory will issue fully compatible blood.

To provide compatible red cells for transfusion the following procedures are undertaken by the Blood Transfusion laboratory:

- ABO and Rh(D) blood group:
 - Major haemolytic transfusion reactions usually result from the transfusion of ABO incompatible blood.
 - The Rh(D) antigen is very immunogenic and the development of anti-D must be avoided in women of childbearing age.
- Antibody screen: excludes the presence of clinically significant red cell alloantibodies in the patient's plasma. These might result in an acute or delayed haemolytic transfusion reaction.
- Selection of appropriate donor units: wherever possible, blood of the same ABO and Rh(D) group as the patient is selected and will be negative for the appropriate antigen if an alloantibody has been identified.
- Cross-match: the patient's plasma is reacted with the donor red cells in vitro. Incompatibility is indicated by agglutination or haemolysis.

A full compatibility procedure is always completed but this can be retrospective if the clinical demand for blood is urgent.

Case history (1)

You are asked to see a 72-year-old man with myelodysplasia who receives regular blood transfusions. One unit of blood was given uneventfully but 15 min into the second unit he began to shiver, felt unwell and developed a pyrexia and tachycardia.

Case history (1) (continued)

A febrile transfusion reaction to HLA or granulocyte antigens is common in multi-transfused patients but cannot be safely distinguished from a haemolytic transfusion reaction due to red cell antibodies without appropriate laboratory tests.

Action

- Stop the transfusion immediately:
 - Replace giving set
 - Keep IV line open with 0.9% saline.
- Check patient identification:
 - Wrist band
 - Compatibility form
 - Compatibility label on unit of blood.
- Take appropriate samples:
 - Blood count
 - Blood cultures
 - Blood transfusion sample
 - Urine for haemoglobin.
- Take samples and a relevant unit of blood to the laboratory.
- Inform haematology medical staff of the problem.
- The laboratory will:
 - Check laboratory documentation
 - Repeat ABO Rh(D) group, antibody screen and cross-match on pre- and post-transfusion samples in parallel
 - Carry out a direct anti-globulin test (DAT or Coombs' test; see Fig. 6.13) to exclude the presence of alloantibodies on the patient's red cells.

Outcome

The red cell alloantibody was identified.

- **Diagnosis.** Haemolytic transfusion reaction.

Monitor renal function, urine output, haemoglobin concentration and check coagulation screen.

A major ABO incompatibility can be life threatening, with acute kidney injury and disseminated intravascular coagulation:

- Monitor as above.
- Insert urinary catheter and monitor urine output.
- Give IV fluids to maintain urine output (> 1.5 mL/h/kg).
- If urine output inadequate insert CVP line and give fluid challenge and diuretics (p. 223).
- Refer to renal unit.
- Report to SHOT (Serious Hazards of Blood Transfusion), a confidential enquiry into major blood transfusion errors in the UK.
 - **Progress.** An error in the collection of the blood from the laboratory led to the wrong blood being given in this man. The error was reported to the hospital as a serious event. The patient maintained his normal blood pressure and his symptoms settled, requiring no further treatment for this.

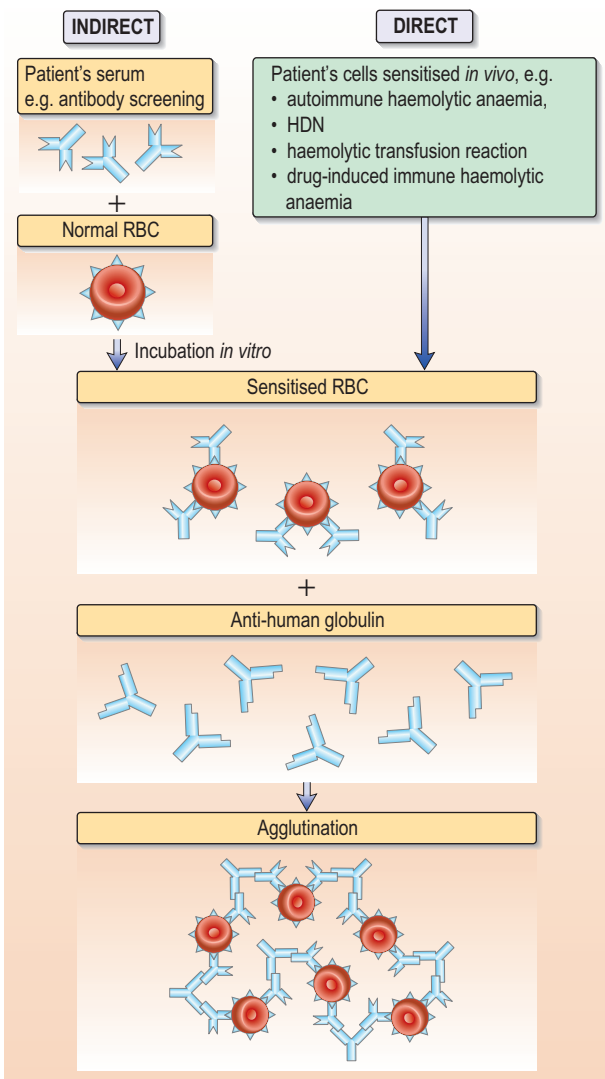


Figure 6.13 Antiglobulin (Coombs') tests. The anti-human globulin forms bridges between the sensitised cells causing visible agglutination. The direct test detects patients' cells sensitised *in vivo*. The indirect test detects normal cells sensitised *in vitro*. HDN, haemolytic disease of newborn.

A major review of blood transfusion procedures was instituted. Fortunately with the prompt treatment, this man had no serious problems.

Other acute complications of blood transfusion can present with:

- Non-haemolytic (febrile) transfusion reactions. These are due to the presence of leucocyte antibodies in a multiply transfused person acting against donor leucocytes in red cell concentrate, leading to release of pyrogens. Leucocyte depleted blood is now used in many countries so the febrile reaction is not often seen.
- Breathlessness:
 - Acute volume overload
 - Transfusion-related acute lung injury (TRALI): characterised by dyspnoea, fever, cough and lung shadowing on CXR.
- Urticaria or anaphylaxis: reaction to plasma proteins.
- Collapse or hypotension: major ABO incompatibility-infected blood product.
- Cardiac arrhythmia:
 - Hypocalcaemia
 - Hyperkalaemia
 - Rapid transfusion with 'cold' blood.

Remember

There are other longer-term complications of blood transfusion including:

- Post-transfusion purpura (PTP)
- Viral infection: hepatitis C, hepatitis B, HIV (*Note: donor blood in many countries checked for these*), CMV
- Iron overload (multiple transfusions)
- Graft versus host disease.

Case history (2)

A 64-year-old man with known severe chronic liver disease on the liver transplant list.

He has been admitted on a number of occasions with haematemesis due to variceal bleeding. Endoscopic banding of the varices has been undertaken and he is on propranolol therapy.

He is admitted on this occasion with a large haematemesis.

On examination he is cold, pale, pulse rate is 120/min and he has a blood pressure of 80/50.

He is in hypovolaemic shock and needs urgent resuscitation with fluid and blood and vasoconstrictor therapy with terlipressin before urgent endoscopy.

Management of massive haemorrhage

- Communicate: nature and urgency of the situation to the laboratory.
- Predict: requirements for blood and blood products; always try to think ahead.
- Monitor:
 - Volume replacement
 - Haemostatic parameters
 - Serum calcium: blood is preserved with citrate-phosphate dextrose solution, which chelates calcium.
- Maintain intravascular volume.
- Avoid:
 - Hypovolaemia
 - Acute kidney injury
 - DIC
 - Cardiac arrhythmias.
- Use:
 1. Saline/colloid solutions
 2. Group 0 Rh(D) negative blood is used
 3. ABO Rh(D) group compatible blood until fully compatible blood available.

Remember

Give blood through a blood warmer to minimise hyperkalaemia and cardiac arrhythmias.

Check for failure of haemostasis

- Initially at beginning of emergency
- Every 5 units of blood given
- Whenever additional blood products (platelets, FFP, cryoprecipitate) are given.

Investigations

Anticipate haemostatic failure. Check:

- Blood count
- PT/INR
- APTT
- Fibrinogen concentration
- Fibrin breakdown products (FDPs or fibrin D-dimers)

Haemostasis failure is due to:

- DIC: secondary to hypovolaemic shock with additional liver failure, infection or tissue trauma
- Dilutional coagulopathy
- Stored blood is depleted of coagulation factors and contains few platelets.

Action

- Request platelets: to maintain platelet count $> 50 \times 10^9/L$ or if sequential platelet counts are falling progressively.
- Request cryoprecipitate (10 units) if fibrinogen concentration $< 1.0 \text{ g/L}$.
- Request fresh frozen plasma (10–20 mL/kg) if PT/INR and PTTK prolonged.

Remember

- Fresh frozen plasma takes 30 min to unfreeze
- Platelets might need to be delivered from Regional Transfusion Centres.

- **Progress.** This man was given 9 units of blood and also balloon tamponade as he was exsanguinating. He could not be resuscitated.

Further reading

Murphy MF, Pamphilon D (eds) 2009 *Practical blood transfusion*. 3rd edn, Wiley-Blackwell, Oxford.

HAEMATOLOGICAL ONCOLOGY

This umbrella term covers a huge range of disorders. There are those that present dramatically and require urgent treatment and, at the other end of the spectrum, there are diseases that are indolent and chronic, often requiring no therapy. You should be able to recognise the low-grade (non-urgent) disease and high-grade (urgent) disorders and refer to your haematology department (outside normal hours do not be afraid to talk to the haematology registrar/consultant on call).

What main groups of disease are there?

- Leukaemias: can be acute (short duration, serious, rapidly fatal if not treated) or chronic. Generally have elevated WBC and other features (see below). These are marrow-/blood-based diseases.
- Lymphomas are lymph-node-based, sometimes involving blood and marrow. Some need urgent treatment and others can be sorted out at leisure.
- Myeloma is a low-grade, highly destructive disorder caused by malignant plasma cells, often presenting with bone pain, renal failure and hypercalcaemia.

Case history (1)

A 63-year-old cleaner is admitted to the medical assessment unit (MAU) with pyrexia and cough productive of sputum. Her general health has been reasonable until now.

On examination she has chest signs suggestive of pneumonia. In addition, she has generalised lymphadenopathy and a

Continued

Case history (1) (continued)

three-fingerbreadth spleen. Scarring over her trunk is, she claims, due to shingles 4 months earlier.

A full blood count shows mild anaemia (Hb 106 g/L), normal platelets, and a WBC elevated at $25 \times 10^9/L$. The haematology technician phones to say most of the white cells are lymphocytes and there are smear cells on the film.

Remember

A smear cell is an artefact induced by making the blood film (the CLL cells are fragile and burst). There are no smear cells actually circulating in the patient's blood.

You need to establish

- Whether this is an acute or chronic disease
- If urgent treatment is required
- What steps you would need to take to make a diagnosis.

The key features

- Old patient
- Fairly well
- Shingles
- Active infection
- Lymphadenopathy/splenomegaly
- High WBC with smear cells.

This must be **chronic lymphocytic leukaemia (CLL)**, the most common leukaemia in adults (Fig. 6.14). It is a slowly progressive disorder and is an incidental finding or presents with an infective complication. Shingles is a fairly common presenting feature.

CLL is a disease mainly of the B lymphocytes (95%, the remaining 5% are T lymphocytes) – determined by checking cell markers. There is a reduction in immunoglobulin synthesis leading to the infective complications.

Other features

- Might be decreased Hb and platelets (depends on disease stage)
- Haemolytic anaemia (red cell autoantibodies)
- Other autoimmune complications.

Management**On day of admission**

Start IV antibiotics (e.g. cefuroxime 750 mg \times 3, erythromycin 500 mg \times 4); rehydrate if necessary. Refer to the haematology department next day.

The prognosis in CLL is very variable and the disease may remain stable for several years. Many patients (approximately 30%) with CLL never need any treatment at all and lead normal lives.

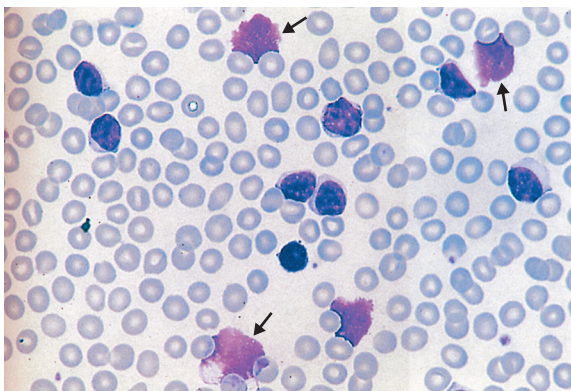


Figure 6.14 Blood film in chronic lymphocytic leukaemia showing numerous smear cells (artefacts).

Long-term treatment

Observation; the patient might require oral chemotherapy at a later stage (e.g. chlorambucil). Rituximab, in combination with chemotherapy, is now first line therapy.

Case history (2)

You are called to see a 43-year-old accountant in A&E. This man went to see his doctor suffering from excessive tiredness. You are presented with an anxious, pale man, who has bruising over his lower limbs and arms. Temperature is 39°C. He is admitted urgently to MAU, where further examination reveals no other signs.

What tests would you arrange?

- FBC and U&Es
- Blood cultures
- MSU
- CXR.

The Hb is 60 g/L, WBC $90 \times 10^9/L$ and platelets are $30 \times 10^9/L$. Renal function is normal and CXR shows minimal increased shadowing at the right base.

Remember

Do not wait until the next morning – the patient may succumb before then!

Is this an acute or chronic disorder?

A short history in an ill patient with severe anaemia and thrombocytopenia indicates an acute disorder.

You must ask what the white cells are, morphologically. If they are neutrophils (neutrophilia), this might reflect an underlying infection; this is unlikely with such a high WBC.

However, the technician looks at the blood film and tells you they look like blasts.

Remember

Blasts are primitive white cells present in bone marrow in small numbers. They are never seen in peripheral blood in health.

This suggests **an acute leukaemia** (Fig. 6.15). In a patient of this age, **acute myeloid leukaemia** is likeliest (if he were a child then acute lymphoblastic leukaemia is more likely).

Investigations

- Specific diagnostic tests (performed by haematology department)
- Peripheral blood film examination (are there Auer rods? If so, their presence confirms AML; these are not all that common)
- Bone marrow aspirate and biopsy
- Cell marker analysis (determines pattern of antigens on white cells)
- Cytogenetic studies on marrow blasts: several karyotypic abnormalities are diagnostic
- Plus other tests, e.g. HLA typing

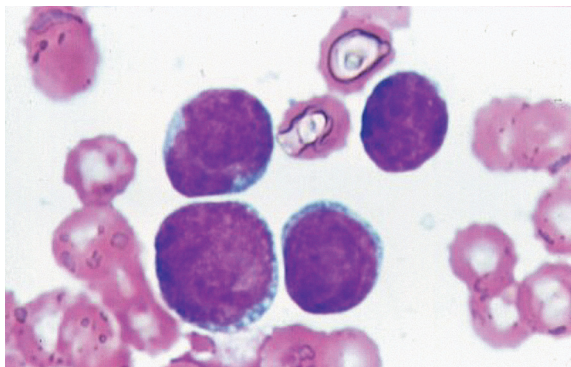


Figure 6.15 Bone marrow in acute myeloid leukaemia showing numerous large leukaemic blasts.

You should aim to perform only the initial treatment steps: IV fluids, empirical (blind) therapy of infection (send blood and urine cultures first) and then notify the haematology staff as soon as possible.

Case history (3)

A 72-year-old butcher is currently on the orthopaedic ward with collapse of one of his lumbar vertebrae. The orthopaedic SHO is concerned because some results have come back which he wishes to discuss with you.

The patient has mild anaemia with an elevated WBC ($26 \times 10^9/L$, mainly neutrophils). The ESR is 120 mm/h. Blood film comment: red cell rouleaux.

There is mild renal impairment and hypercalcaemia (corrected calcium is 3.21 mmol/L).

The patient appears quite uncomfortable and has lower back pain, pain in the left rib cage, right humerus and right thigh. His general health was excellent until about 4 months ago when he developed anorexia and mild weight loss. His wife, who is present, is concerned as he is forgetful and confused at times (this has been much worse over the past 1–2 weeks).

What possible diagnoses are there?

Although not in extremis, this man is ill:

- An ESR of 120 suggests serious underlying pathology (an ESR of 120 could be due to serious infection, autoimmune disease, rheumatoid disease, malignancy).
- Red cell rouleaux, renal impairment and hypercalcaemia in a patient with bone disease suggest either a primary bone disorder (such as myeloma) or possible infiltration by malignancy, e.g. carcinoma.

If outside working hours there is little else you can request. Your main objective is to treat the symptoms, e.g. rehydrate, start antibiotics if you think infection is present, correct the elevated calcium level (see p. 450). Alert the haematology team.

As soon as possible, check:

- Blood film.
- Immunoglobulin levels/serum protein electrophoresis/immunofixation.
- Repeat biochemistry to check renal function and calcium level.
- Send urine for Bence-Jones protein and plasma for free immunoglobulin light chains.
- Blood cultures if febrile.
- MSU.
- Arrange skeletal survey (plain radiology of skull, spine, pelvis, femora).

In this case the results are:

- Elevated total IgG with reduced IgA and IgM.
- Serum IgG M paraprotein (paraprotein = monoclonal immunoglobulin produced by the malignant clone of plasma cells).
- Bence-Jones protein present: kappa light chains.

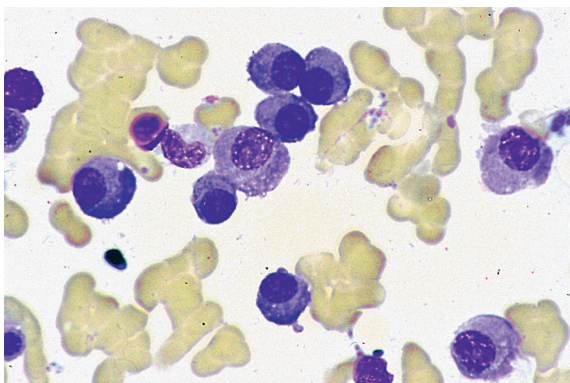


Figure 6.16 Bone marrow aspirate in myeloma showing large numbers of plasma cells.

- Widespread lytic lesions throughout skeleton.
- Subsequent bone marrow aspirate showed infiltration by abnormal plasma cells (Fig. 6.16).
 - *Diagnosis.* Multiple myeloma.

The patient should be referred for specialist advice, i.e. treatment for his myeloma. He also needs bisphosphonate treatment for his bone disease and orthopaedic referral for possible kyphoplasty, which involves inflating a balloon in the affected vertebral body and filling this, with methyl methacrylate cement in order to restore the vertebral shape.

Case history (4)

A 50-year-old bank manager is admitted with weight loss, sweats and splenomegaly.

On examination initial investigations show mild anaemia, WBC $200 \times 10^9/L$ and platelets $600 \times 10^9/L$.

What further information do you require?

- White cells: are they blasts? No – there are neutrophils, eosinophils, basophils and early (i.e. immature) granulocytes (e.g. promyelocytes, myelocytes).
- How large is the spleen? Palpable to umbilicus (ultrasound = 24 cm).

Biochemical screen

- Normal apart from elevated serum uric acid level.
- Re-examine patient yourself. Are there any other abnormal findings?
- There is no lymphadenopathy.
- Liver edge is palpable.
- Chest is clear.
- Fundi: NAD.

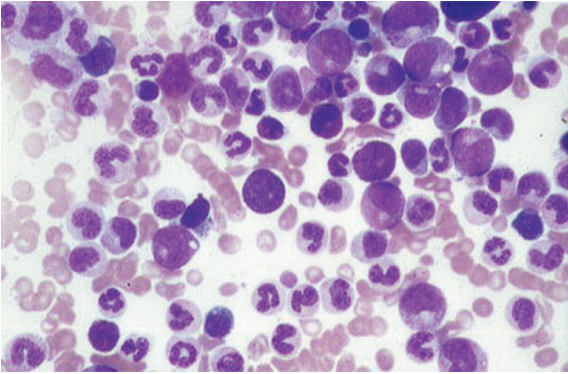


Figure 6.17 CML blood film: note the large numbers of granulocytic cells, in particular neutrophils, at all stages of development.

What is the underlying diagnosis?

There are several significant findings, i.e. very high WBC, splenomegaly with weight loss and sweats. Could the patient have an underlying infection/neoplasm producing these features (i.e. reactive process)? Yes, but it is much more suggestive of an underlying primary blood disorder such as **chronic myeloid leukaemia**, because the white cell count is high with the whole spectrum of granulocytic cells present (Fig. 6.17). If the blood picture were 'reactive', a neutrophilia would be more likely.

What single investigation will confirm the diagnosis?

Cytogenetic analysis of peripheral blood white cells or bone marrow white cells.

The Philadelphia chromosome will be present (translocation of DNA between chromosomes 9 and 22) in most (95%) CML.

Remember

Philadelphia chromosome is present in some acute leukaemias but this patient does not have features of acute leukaemia, and the bone marrow will confirm this.

Does he need urgent referral to the haematology team?

Unless the patient is very unwell or has features of leucostasis (blood sludging in the lungs or brain due to high WBC) then there is no immediate need for urgent referral, but you should alert the haematology staff, who should take over the patient's care next day. Leucostasis can result in:

- Confusion
- Visual disturbance
- Cough and dyspnoea.

Features suggestive of acute leukaemia/high-grade lymphoma

- Acute onset
- Unwell
- Dramatic presentation
- Extensive infection and/or bruising
- Gum swelling
- Fundal haemorrhage
- Coagulopathy
- Blasts/immature cells in peripheral blood
- Auer rods (neutrophil granules join up to produce these rod-like structures = pathognomonic of acute myeloid leukaemia (AML)).

Features suggestive of chronic/low-grade haematological malignancy

- Less dramatic onset
- Not particularly unwell
- Previous infection (e.g. chest infection or herpes zoster)
- Absence of blasts in blood
- Abnormal peripheral blood cells: lymphocytes with abnormal morphology or immature granulocytes. Generalised lymphadenopathy present for months.

Refer all suspected patients with acute leukaemia to the haematology team as soon as possible, for specialist management.

Remember

The WBC does not have to be high to diagnose acute (or chronic) leukaemia. In many cases acute leukaemia may present with normal or low WBC.

Not all patients with acute leukaemia are ill at presentation.

Is it lymphoma or leukaemia? (Fig. 6.18)

- Leukaemias generally involve bone marrow and blood. Lymph nodes and other organs might be involved.
- Lymphomas originate in lymphoid tissue (lymph nodes, spleen), sometimes spill over into blood and might involve marrow (especially low-grade lymphomas).
- High-grade lymphoma and acute lymphoblastic leukaemia are very similar.
- Low-grade lymphomas and chronic lymphoid leukaemias are similar.
 - **Progress.** This patient with chronic myeloid leukaemia was referred to the haematologists, who treated him with Imatinib. He achieved a complete haematological response.

Further reading

Appelbaum FR, Rowe JM, Radich J, Dick JE. Acute myeloid leukemia. *Hematology (American Society of Hematology Educational Program)* 2001; Review: 62–86.

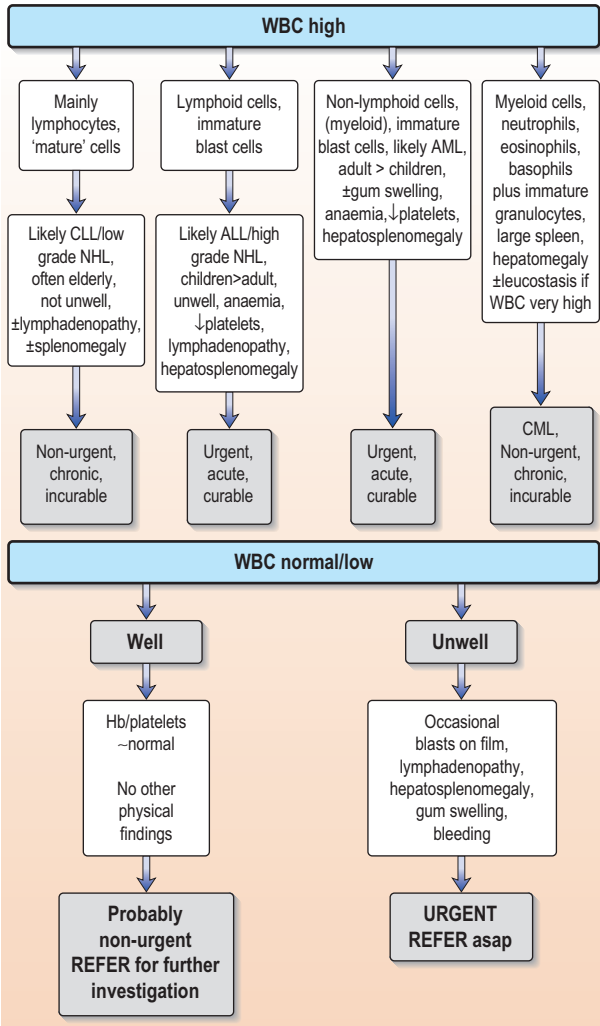


Figure 6.18 Summary of suspected haematological malignancy (ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin's lymphoma).

- Magrath IT, Boffetta P, Potter M (eds) 2010 *The Lymphoid neoplasms*. 3rd edn, Hodder Arnold, London.
- Sawyers CL. Even better kinase inhibitors for chronic myeloid leukaemia. *N Engl J Med* 2012; **362**: 2314–2315.

ANAEMIA IN RHEUMATOID ARTHRITIS

Case history

A 53-year-old woman with rheumatoid arthritis was admitted for investigation of anaemia.

On examination she had typical features of rheumatoid arthritis in her hands and arms. Her hands are grossly deformed, swollen with redness over the MCPs. She has tender, subcutaneous nodules on her elbows. All these features were indicative of an acute flare-up of her condition.

Investigations showed a Hb of 92 g/L, MCV 84 fL, WBC $11.4 \times 10^9/L$ and platelets $490 \times 10^9/L$. Serum vitamin B₁₂, folate and ferritin were checked and found to be normal.

There are several possible causes for this anaemia:

- Bleeding (e.g. due to NSAIDs): the patient denies obvious GI bleeding. If she had been bleeding chronically her MCV would probably be reduced (iron deficiency). This woman's MCV is normal, making chronic blood loss unlikely.
- Poor diet: can induce folate deficiency, but we know her folate level is normal.
- Autoimmune causes: e.g. pernicious anaemia (PA; she has rheumatoid arthritis (RA) and might possibly have PA, another associated autoimmune disease). However, her vitamin B₁₂ level is normal.
- Felty's syndrome (p. 123): RA, splenomegaly and neutropenia. This woman has no features of this disorder.
- Infiltrations, myelodysplasia (MDS): difficult to exclude these in the absence of additional information, e.g. bone marrow. In MDS and marrow infiltration due to carcinoma in the presence of reduced Hb, it is likely (but not always the case) that the blood film would show morphological abnormalities such as red cell 'tear-drop' cells, nucleated red cells, hypogranular neutrophils, immature white cells. This woman's blood film simply showed RBC rouleaux.
- Renal impairment, liver disease: again, morphological abnormalities are usually present on the film, and biochemical screen will assess liver and renal function.
- Drug-induced anaemia: several mechanisms, e.g. haemolysis. There are no features suggesting this. Remember the bone marrow suppressive effect of gold and azathioprine.

This woman's ESR was found to be > 100 mm/h with a high C-reactive protein. Her rheumatoid disease was very active (flare-up) and 3 months before admission her Hb was 110 g/L. The drop in Hb has coincided with the flare-up; a common finding, especially in patients with rheumatoid arthritis.

A major diagnostic pitfall in the assessment of anaemia in patients with inflammatory disease is in the determination of iron status. Patients can be iron deficient (confirmed by bone marrow aspirate stained for iron, the 'gold standard') yet have a normal serum ferritin: an acute-phase protein that rises to normal (or > normal) in such patients.

Assessment of iron status in patients with inflammatory disorders

- Ferritin: likely to be misleading for the reasons given above.
- Serum iron/TIBC: might show reduction of both in chronic disease. These tests are seldom performed now because they are unreliable. Ferritin is the preferred assay.
- Bone marrow: will determine iron status, but is expensive, painful and to be avoided if possible.
- Serum transferrin receptor assay: number of transferrin receptors on red cells rises in iron deficiency but remains normal in secondary anaemia. This test is replacing bone marrow aspirate in diagnosis of iron deficiency in patients such as this.

This woman had normal transferrin receptor levels, confirming anaemia of chronic disease. She failed treatment with sulfasalazine and methotrexate. She was therefore treated with Etanercept, a fully humanised p75 TNF α receptor IgG fusion protein subcutaneously, with a good response in her joints and the ESR. She is now attending the Rheumatology Clinic for follow-up.

Anaemia in chronic kidney disease (CKD)

The kidney is the body's major site of erythropoietin (Epo) production. In renal disease Epo levels fall, leading to chronic anaemia.

Additional factors in development of anaemia in CKD

- Reduced RBC lifespan
- Iron deficiency (blood loss in dialysis tubing or GI tract blood loss)
- Folate loss due to dialysis.

What features should you look for?

- Low Hb
- Normal MCV
- Reticulocytes normal or reduced: low Epo reduces RBC production.
- Bizarre RBC shape on blood film: burr cells.

Management

Generally, Epo replacement given at dialysis improves the Hb in these patients (50–100 units/kg \times 3 per week IV). Alternatively, darbepoietin alfa can be given weekly or pegzerepoietin alfa monthly. Might also require additional iron and folic acid. The Hb should be kept within the range of 100–120 g/L.

Anaemia in liver disease

Complex and multifactorial

Patients with chronic liver failure generally have moderate anaemia.

The red cells are often macrocytic and can have abnormal shapes – target cells and spur cells – owing to membrane abnormalities.

Vitamin B₁₂ levels are normal or high; folate levels are often low, owing to poor dietary intake.

- Bleeding produces a hypochromic, microcytic picture.
- Alcohol causes macrocytosis, sometimes with leucopenia and thrombocytopenia due to bone marrow suppression.
- Hypersplenism results in pancytopenia.
- Cholestasis can often produce abnormal-shaped cells and also deficiency of Vitamin K.
- Haemolysis accompanies acute liver failure and jaundice.
- Aplastic anaemia is present in up to 2% of patients with acute viral hepatitis.
- A raised serum ferritin with transferrin saturation (> 60%) is seen in hereditary haemochromatosis.

ANAEMIA IN CANCER

Case history

A 55-year-old woman who underwent a right mastectomy 10 years earlier presents with a subcapsular fracture of the left humerus. This had followed minimal trauma following slipping on the floor in the supermarket. It was thought that she might have disseminated bony metastases.

The contributory information provided by the blood count is shown below:

- Hb 86 g/L
- MCV 76 fL
- WBC $14.7 \times 10^9/L$
- Platelets $64 \times 10^9/L$
- Reticulocytes 2.0%
- Nucleated red cells
- Occasional myelocytes noted 4/100 WBCs
- Rouleaux +
- Platelets clumped + +

Information

Rouleaux

The tendency of red cells on the blood film to stack up like a 'pile of coins' relates to an increase in plasma proteins, particularly fibrinogen, as part of the acute-phase response.

This patient has a microcytic anaemia with rouleaux formation on the blood film. The anaemia of chronic disorder is common in disseminated malignancy and many other inflammatory and infective illnesses.

Further investigations

● Blood

- Serum alkaline phosphatase 247 IU/L
- CRP 80
- Serum calcium 2.9 mmol/L.

● Imaging

- X-ray of shoulders showed humeral fracture
- Skeletal survey showed bony metastases in thoracic spine and pelvis.
 - *Diagnosis.* Carcinoma of the breast with bony secondaries.

Anaemia of chronic disorder: pathophysiology

- Functional iron deficiency
- Reduced sensitivity to erythropoietin
- Reduced red cell lifespan.

She has a raised total white cell count with nucleated red cells and immature granulocytes seen on the blood film. This is a **leucoerythroblastic picture**; such cells are normally confined to the bone marrow. Bone marrow infiltration by disseminated malignancy disrupts the normal mechanisms controlling release of haemopoietic cells into the blood.

Leucoerythroblastic anaemia

Causes include:

- Acute haemolysis
- Severe infection
- Severe hypoxia
- Bone marrow infiltration:
 - Carcinoma
 - Myeloma
 - Lymphoma
 - Tuberculosis
 - Myelofibrosis
 - Osteopetrosis.

Remember

Most blood count analysers cannot distinguish nucleated RBCs (nRBCs) from white cells, and when nRBCs are present might give an inappropriately high white cell count. Ask for the blood film to be reviewed.

The reticulocyte count is not increased and no red cell fragmentation is present on blood film review. Microangiopathic haemolytic anaemia (MAHA), which sometimes complicates disseminated breast, prostate or gastric carcinoma, is not likely to be a feature in this patient. MAHA results from mechanical disruption of red cells in small blood vessels and can be complicated by chronic DIC, with a coagulopathy, reduced fibrinogen concentration, elevated fibrin breakdown products and thrombocytopenia.

Remember

Before accepting that a patient is thrombocytopenic:

- Ask for the blood film to be reviewed
- Repeat the blood count: fibrin formation or a small clot in the sample will result in a low platelet count.

This patient has thrombocytopenia. The aetiology of thrombocytopenia in disseminated malignancy is complex and can be due to:

- Bone marrow infiltration
- Folate deficiency secondary to anorexia
- Cytotoxic chemotherapy
- DIC.

However, review of the blood film in this patient reveals that the thrombocytopenia is spurious – platelets are clumped on the blood film. Platelet clumping is a common phenomenon related to the EDTA anti-coagulant that blood is collected into.

Progress and management

This lady was treated symptomatically with NSAIDs and started on bisphosphonates. She was referred to the Oncology Department for an MDT for discussion of further management.

INFECTION/SEPSIS

Bacterial sepsis

This results in a characteristic constellation of changes in the blood which provide confirmatory evidence of sepsis and, in occasional patients with occult infection, may direct appropriate investigations.

- Neutrophil leucocytosis: increased numbers of neutrophils.
- Immature granulocytes (= left-shift): occasional promyelocytes, myelocytes.
- Toxic granulation: coarse neutrophil granulation.
- Döhle bodies (these are white cells containing large RNA inclusions that are seen in, e.g., sepsis, malignancy, pregnancy).

Remember

A neutrophil leucocytosis may reflect processes other than infection:

- Tissue ischaemia:
 - Myocardial infarct
 - Sickle-cell crisis
- Inflammation:
 - Rheumatoid arthritis
 - Vasculitis
- Endocrine disease:
 - Thyrotoxicosis
 - Cushing's disease
 - Post-splenectomy

Uncontrolled sepsis might be accompanied by:

- A falling white cell count/neutropenia
- Granulocyte vacuolation
- Bacteria visible on the stained blood film
- Thrombocytopenia
- DIC.

Anaemia is common in bacterial sepsis and is usually related to the acute-phase response. Occasionally, haemolysis and red cell fragmentation accompany DIC, and severe haemolysis might complicate *Clostridium welchii* septicaemia with spherocytosis on the blood film.

Malaria (see also case on p. 14)

This should be suspected in any individual with a fever who has recently visited/come from malarial parts of the world. Thrombocytopenia is a frequent accompaniment of malaria infection and haemolytic anaemia might develop, particularly if an individual also has G6PD deficiency.

Remember

If malaria is suspected:

- Ask for thick and thin blood film examination
- Repeat \times 3–5 if the initial results are negative but clinical suspicion persists.

If malaria is diagnosed:

- Ask for the species of *Plasmodium*
- If *P. falciparum*, ensure you are given the parasite count. This indicates the severity of infection:
 - A high parasite count $>$ 5.0% indicates an increased risk of cerebral malaria
 - Pre-schizont forms indicate an increased risk of cerebral malaria.

Some features of severe falciparum malaria

Remember

Treatment for severe malaria due to *P. falciparum* is a MEDICAL EMERGENCY. Give:

- Artesunate 2.4 mg/kg single bolus and then at 12 h and 24 h and then daily until oral medication can be tolerated.
- Quinine dihydrochloride 20 mg/kg IV over 4 h, then 10 mg/kg if artesunate unavailable.

See National Formulary for details; see p. 15 for other treatment.

- CNS: cerebral malaria (coma, convulsion)
- Renal:
 - Haemoglobinuria (blackwater fever)
 - Oliguria
 - Uraemia (acute tubular necrosis).

- Blood:
 - Severe anaemia (haemolysis and dyserythropoiesis)
 - Disseminated intravascular coagulation (DIC: haemorrhage).
- Respiratory: acute respiratory distress syndrome (see p. 391).
- Metabolic:
 - Hypoglycaemia (particularly in children)
 - Metabolic acidosis.
- Gastrointestinal/liver
 - Diarrhoea
 - Jaundice/splenic rupture.
- Other:
 - Shock: hypotensive
 - Hyperpyrexia.

Beware

The parasite count in falciparum malaria may underestimate the severity of the infection due to parasite sequestration. Always take a diagnosis of falciparum malaria seriously.

Viral infections

These produce a variety of specific and non-specific effects on the blood that might be helpful diagnostically.

Information

Consider:

- Age of patient
- Length of history
- Clinical findings
- Morphology of lymphoid cells
- Monospot or Paul–Bunnell test
- Immunophenotyping

Non-specific effects

These are common to many viral illnesses:

- Mild neutropenia and thrombocytopenia
- Occasional reactive lymphoid cells on blood film.

Specific effects

- *Glandular fever* is produced by Epstein–Barr virus infection (see p. 18). Similar features are seen in cytomegalovirus but also in toxoplasmosis. The reactive lymphocytosis must be distinguished from a malignant lymphoid proliferation.
- *Erythrovirus B₁₉* causes Fifth's disease and specifically infects erythroid progenitor cells, resulting in transient erythroid hypoplasia and failure of red cell production. This is of no consequence in otherwise healthy individuals but, in those with chronic haemolytic anaemia, it causes a sudden fall in the haemoglobin concentration, with absent reticulocytes. Urgent blood transfusion can be life saving.

Remember

Erythrovirus B₁₉ is infective, and chronic haemolytic anaemias can be inherited, e.g. sickle-cell disease. Ask about other family members with haemolysis, 'Are they well?'

- *HIV infection* results in anaemia, thrombocytopenia and neutropenia in most patients. The severity of the cytopenia is related to the stage of the disease and is reflected by ineffective haemopoiesis with dysplastic changes in bone marrow precursor cells. It can be exacerbated by inter-current infection and therapy.

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BLACKOUTS

This implies either altered consciousness, with or without falling, or sometimes a visual disturbance.

Case history

An 86-year-old woman is brought into A&E with a 'blackout'. She had been found on the floor but had regained consciousness on the way to hospital.

On examination pulse and blood pressure were normal and there was no abnormality found on neurological examination.

What should you ascertain from the history?

- Any previous episodes?
- What was patient doing at the time (e.g. micturition, change in posture, coughing).
- Symptoms preceding blackout:
 - Chest pain or palpitations, suggests cardiac cause.
 - Aura, suggests epilepsy.
- Witness history: any witness(es) to give description of the blackout.
 - **Differential diagnosis.** Common causes include neurological or cardiovascular events.

Epilepsy in the elderly

- Focal fits or a focal origin of generalised seizures are common in the elderly (accounting for 80% of fits in this age group).
- Post-ictal confusion, headache and focal signs (Todd's paresis) are common.
- 35% to 50% of fits in the elderly are caused by vascular disease.
- 20% of patients with stroke have seizures within the first year.
- Elderly persons are more susceptible to pharmacological causes of fits, e.g. neuroleptics, tricyclics, and to alcohol withdrawal.
- An EEG can be useful but a normal or non-diagnostic EEG does not rule out epilepsy.
- Don't forget hypoglycaemia as a cause of fits.
- Anti-convulsant drugs should be started after the first fit if a vascular or structural cause is suspected.
- Pallor suggests cardiac cause.
- Tonic-clonic contractions or incontinence suggest epilepsy.
- Was there a history of head turning or tight neckwear? This suggests carotid sinus syndrome.

- Was there a period of drowsiness after blackout? This suggests epilepsy but might also occur in cardiac causes.

Remember

Epilepsy might be secondary to reduced cardiac output.

Investigations

- FBC, U&Es, glucose, TFTs, Ca²⁺
- ECG
- 24-hour tape if ECG abnormal or history suggestive of cardiac cause
- If history suggests epilepsy: EEG, and/or CT scan
- Specialist intervention: carotid sinus massage – undertaken if carotid sinus syndrome suspected (*Note: contraindications for massage include presence of carotid bruit or history of carotid territory neurological events*)

Cardiovascular causes of blackouts

- Arrhythmias (brady- or tachy-) can be difficult to diagnose and sometimes require repeated 24-h tapes or 2–3-week ‘event recorders’ (see p. 278).
- Myocardial infarction: can be pain free in older people.
- Aortic stenosis: typically causes exertional syncope, also shortness of breath on exertion and angina.
- Hypertrophic cardiomyopathy: diagnosed on echocardiogram.
- Postural hypotension.
- Carotid sinus syndrome is an underdiagnosed cause of unexplained blackouts. It is caused by an exaggerated response of baroreceptors in the carotid sinus and requires specialist investigation by carotid sinus massage with close observation. There are three variants. The **cardioinhibitory variant** is diagnosed by > 3-s asystole on massage. The **vasopressor variant** is diagnosed by a 50-mmHg drop in blood pressure or systolic blood pressure drop to < 90 mmHg. Thirdly, up to one-third of cases are mixed.
- Vasovagal syncope: occasionally presents for the first time in older people. Consider if there is a long history of ‘funny turns’.

Treatment

In this patient an ECG, chest X-ray and blood tests were normal. It was thought that the **blackout could be due to an arrhythmia** so a 24-hour tape ECG was performed. This showed episodes of tachycardia, bradycardia, with two episodes of sinus arrest, compatible with the **sick sinus syndrome**.

- **Progress.** This patient was fitted with a pacemaker/DDI and has had no further attacks.

Further reading

Fall Prevention in Acute Care Hospitals: A Randomized Trial.
Dykes PC, Carroll DL, Hurley A et al. JAMA 2010; 304(17): 1912-1918.

FALLS IN THE ELDERLY

Case history

A 79-year-old man was brought into A&E following a fall. He was taking atenolol 100 mg daily, aspirin 75 mg daily and bendroflumethiazide 2.5 mg daily.

On examination he was well. His pulse was normal, blood pressure low at 90/50 but no abnormal neurological signs. He had symptomatic **postural hypotension** on standing up.

What questions should you ask?

- What was he doing when he fell, e.g. was there a postural element?
- What does he remember about the fall?
- Did he lose consciousness?
- What happened immediately before the fall?
- Were there any preceding symptoms?
- Was there a witness?
- Were there any physical hazards, e.g. wet floor, carpet edge?
- Had he fallen before?

These features can help distinguish pathological causes (intrinsic) from those with a major external factor (extrinsic), although in practice most falls are multi-factorial. Falls or 'collapse' can be seen as a final common pathway for many diseases common in the elderly.

Falls – examination

Full physical examination, especially:

- Cardiovascular:
 - BP including postural changes after 1-3 min
 - Evidence of heart failure or rhythm disturbance
 - Murmurs.
- Musculoskeletal:
 - Arthritis: acute or chronic and evidence of joint instability
 - Muscle wasting, especially quadriceps.
- Neurological:
 - Focal signs, don't forget cerebellar/brainstem
 - Hearing or visual impairment
 - Gait: observation of the patient standing from sitting (with arms folded) and walking (with turns) provides a good assessment of risk for falling.

Orthostatic hypotension

This is defined as a > 20-mmHg drop in systolic BP on standing or during head-up tilt:

- Common in elderly: occurs in up to 30% of healthy older people and it is not clear why some develop symptoms.
- 'Physiological' changes in elderly: decreased baroreceptor sensitivity increases risk of postural hypotension.
- 'Pathological' changes: e.g. sepsis with vasodilatation; poor LV function; neurological disease affecting reflex pathways.
- Pharmacological causes: beta blockers, vasodilators, anti-parkinsonian drugs, sedatives, neuroleptics, diuretics.

Investigations of falls

- BP and heart rate measurement with patient lying flat, with patient standing upright or at 45° on tilt table after 1, 3 and 5 min.
- FBC for evidence of infection, anaemia.
- U&Es, creatinine for evidence of dehydration, renal impairment (eGFR is calculated).
- Blood glucose for hypo-/hyperglycaemia.
- Thyroid function tests for subclinical hypothyroidism.
- CXR for infection, tumour.
- ECG for ischaemia, arrhythmias, silent MI.
- Heart beat monitoring (beat-to-beat variation) for autonomic neuropathy.
- MSU and Stix testing for infection.

Management of falls

- Review medications and withdraw exacerbating drugs if possible.
- Treat medical factors, e.g. sepsis.
- Assessment and reduction of osteoporosis risk.
- Advice to patients (see below).
- Drug treatment occasionally used in patients with persistent disabling symptoms:
 1. Fludrocortisone 100–200 µg at night. Watch for fluid retention and hypokalaemia
 2. If still symptomatic, add sympathomimetic agent, e.g. ephedrine 15 mg × 3 daily. This can be increased to 45 mg × 3 (side effects: hypertension, tachycardia, tremor).
 - **Progress.** In this patient with postural hypotension, the atenolol was stopped and a careful watch was kept on his blood pressure (he had his own blood pressure machine) over the following few weeks. He should stay on aspirin and bendroflumethiazide. His BP stabilized at 115/80 and therefore no further medication was required.

Advice for patients with postural hypotension

- Get out of bed in stages.
- Pause between positional changes.
- Wear leg support tights during day; take them off at night.
- Raise head of bed.
- Avoid alcohol.

Further reading

www.profane.eu.org Prevention of falls network Europe; focuses on the prevention of falls.

DELIRIUM (see p. 515)

This is also known as 'toxic confusional state'. It is the commonest psychosis seen in the general medical setting. It is 'brain failure' with impairment of attention and abnormalities of perception and mood.

Case history

A 76-year-old female is admitted to MAU with a 3-day history of confusion associated with hallucinations.

On examination she has signs of consolidation at the left lung base. Her temperature and white cell count, however, were within normal limits.

Delirium in the elderly

An elderly person presenting with acute confusion associated with disorientation, agitation \pm hallucinations is a common medical emergency. In a hospital setting, the elderly develop delirium while receiving treatment for other medical or surgical problems, the reported incidence varying from 10 to 60%.

As a condition (syndrome) it is associated with increased morbidity and mortality.

Diagnosis

Use DSM (IV-TR) criteria or the Confusional Assessment Method (CAM), which is based on the DSM criteria (see below).

Delirium – diagnostic criteria (derived from DSM-IV-TR)

- Disturbance of consciousness:
 - clarity of awareness of environment
 - ability to focus, sustain or shift attention
- Change in cognition:
 - memory deficit, disorientation
 - language disturbance, perceptual disturbance
- Disturbance develops over a short period (hours or days)
- Fluctuation over course of day

Information

The Diagnostic and Statistical Manual (DSM) is published by the American Psychiatric Association and provides clear descriptions of diagnostic categories. The 4th edition (DSM-IV-TR) was published in 2000. The 5th edition will be available in 2013.

Confusional assessment method (CAM) criteria

Need points 1 and 2:

1. *Acute onset + fluctuating course*: this history is usually obtained from the family/carer or from the nurse caring for a patient already in hospital.
2. *Inattention*: is the patient easily distractible or does he/she have difficulty keeping track of what is being said?
... and either 3 or 4:
3. *Disorganised thinking*: is the patient incoherent? Is the conversation irrelevant?
4. *Altered level of consciousness*: the patient might be hyperactive, hypoactive/lethargic or semi-conscious.

Remember

- One in four patients with delirium are hypoactive
- Although history/observations can confirm the presence of CAM features, it is also useful to assess the patient's cognitive functioning using serial mental test scores, e.g. Abbreviated Mental Test (AMT) (Table 7.1). Other tests using questions on: orientation (e.g. time, place, date), registration (naming objects), attention and calculation (simple arithmetic), recall (previously mentioned objects) and language (understanding commands) can be used.

What should you do when delirium is suspected/diagnosed?

- Identify the cause by taking a medical history, physical examination and appropriate investigations.
- Manage the delirium.

Medical history

Illness in old age can present in a non-specific or atypical way. It is therefore necessary to go through a systematic enquiry to detect symptoms of physical illness, particularly those relating to chest infection and urinary tract infection. The family/carer or doctor should also be questioned about recent changes to drug therapy.

Table 7.1 Abbreviated Mental Test (AMT)

Total score ten (one point for each item)

- Age
- Time (to nearest hour)
- Address for recall
- Year
- Where do you live (town or road)?
- Recognition of two persons
- Date of birth (day and month)
- Year of the start of the First World War
- Name of present leader of the country
- Count backwards 20 to 1

Physical examination

Full physical examination including neurological examination is essential as any physical illness in older people can lead to delirium.

Investigations

- FBC
- U&Es
- Liver function tests
- Calcium
- Phosphate
- Thyroid function tests
- CXR
- ECG and MSU
- Other investigations as indicated by clinical findings

Causes

For causes, remember the mnemonic **delirium** and think of common conditions:

- D** drugs: side effects, toxicity of drugs, e.g. hypotensives, sedatives
- E** electrolyte/endocrine disturbance, e.g. hyponatraemia, hypernatraemia, hypothyroidism
- L** lack of drugs: withdrawal of drugs
- I** infections, e.g. pneumonia, cellulitis
- R** reduced sensory input, e.g. visual impairment
- I** intracranial: TIAs, epilepsy
- U** urinary retention/faecal impaction
- M** myocardial: ischaemia/infarct, arrhythmias, CHF.

Remember

The presentation of illness in the elderly can be altered, e.g. not all patients with pneumonia will have a raised temperature or raised white cell count.

Risk factors for delirium

- Dementia
- Severe physical illness
- Raised urea/creatinine
- Visual impairment
- More than three prescribed drugs.

How would you manage a patient with delirium?

- Treat cause(s) of delirium. Review present drug therapy.
- Environmental measures and general support: fluids/nutrition; bladder/bowel care + environment (nurse in quiet, dimly lit room if possible), providing reassurance and reorientation.

- Pharmacological management: only appropriate if general supportive measures are not adequate to reduce patient's distress and if there is danger to patient. Drugs of choice:
 1. Lorazepam up to 2 mg IV or IM up to 4-hourly
 2. Haloperidol 0.5 mg IV or IM, repeating if necessary after 30 min
 3. Olanzapine 5 mg is also used.
- **Progress.** In this patient the cause of her delirium was pneumonia. She did not mount a raised white count or have a temperature. Her delirium resolved on treatment with antibiotics.

Further reading

Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12** (3): 189–198.

Inovye SK. Delirium in the older persons. *NEJM* 2006; **354**: 1157–1185.

Young J, Inovye SK. Delirium in older people. *BMJ* 2007; **334**: 824–826.

Help website. <http://hospitalelderlifeprogram.org>

DEMENTIA

- **Definition.** Dementia is defined by the Royal College of Physicians as global impairment of higher cortical functions, including memory:
 - The capacity to solve problems of day-to-day living.
 - The performance of learned perceptuomotor skills.
 - The correct use of social skills.
 - The control of emotional reactions in the absence of gross clouding of consciousness.

Case history

An 89-year-old man with a 6-month history of deteriorating short-term memory and increasing confusion is referred to A&E because of self-neglect. He has become even more confused over the previous 24 h. He was diagnosed as having **dementia** and referred to the Care of the Elderly team.

Remember

You should distinguish delirium from dementia, but remember that delirium can and does occur commonly in patients with dementia, as in this case.

- Dementia is often irreversible and progressive, and has a number of causes.
- Assessment: this is performed using the 10-point Abbreviated Mental Test (AMT; Table 7.1), or Clock-drawing test (Fig. 7.1).
- Although screening tests are useful in demonstrating the presence of deficits in cognition, they cannot be used for making the diagnosis of dementia or identifying the underlying cause. This requires imaging (CT or MRI scan) and, in some patients, assessment by a clinical

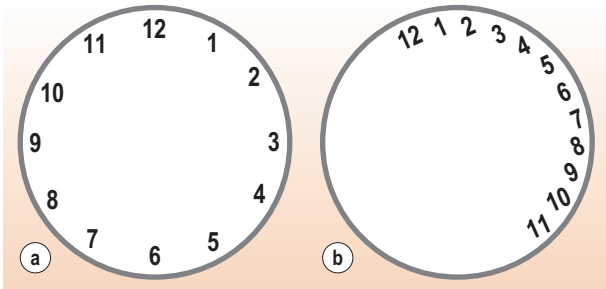


Figure 7.1 Clock drawing test. (a) Normal. (b) Abnormal – inappropriate spread.

psychologist and/or a psychiatrist. A history of progressive decline in memory or cognition over 6 months is significant.

Investigations

Initial investigations for dementia:

- FBC and film
- U&Es
- Random blood glucose
- LFTs
- Thyroid function tests (TFTs)
- Vitamin B₁₂ and folate
- Syphilis serology
- CXR
- ECG
- CT/MRI scan of brain or PET scan

Causes

The common causes of dementia include Alzheimer's disease, multi-infarct dementia, Lewy body dementia and Creutzfeldt-Jakob disease, but other conditions can produce a dementia-like syndrome (Table 7.2) and p. 523.

Table 7.2 Examples of treatable causes of dementia-like syndrome (see also p. 523)

Hypothyroidism
 Vitamin B₁₂ deficiency
 Folate deficiency
 Recurrent hypoglycaemia
 Alcohol excess
 Depression ('pseudodementia')
 Subdural haematoma
 Normal pressure hydrocephalus

Management

- Alzheimer's disease (AD): although there is no cure for Alzheimer's disease, research on acetylcholine esterase inhibitors has shown that in selected patients with mild to moderate AD the decline can be slowed down. The National Institute for Clinical Excellence (NICE) has produced a guidance on use of donepezil, rivastigmine, memantine and galantamine in patients with mild to moderate AD by specialists. Other agents/drugs that have some benefit to patients with AD include vitamin E and *Ginkgo biloba* extract.
- Multi-infarct dementia: treat the risk factors, such as hypertension. Aspirin also has a role in preventing further strokes. *Ginkgo biloba* (120–240 mg daily) can also help.
- As dementia progresses, the management focus changes to care provision for patients plus support for carers.
- Lewy body dementia: avoid anti-psychotics as they can increase confusion. Some of these patients respond to acetylcholine esterase inhibitors.

Remember

Acetylcholine esterase inhibitors for Alzheimer's disease are initiated only by a specialist (psychiatrist, neurologist or a geriatrician):

- Donepezil 5–10 mg daily
- Rivastigmine 3–12 mg daily
- Galantamine 8–24 mg daily
- Memantine 5–20 mg daily.

- **Progress and management.** In this patient, his previous history of hypertension and two small strokes suggested a multi-infarct dementia (avascular dementia). The diagnosis was confirmed by an MRI. The Care of the Elderly team arranged for full support in the community and he was continued on his treatment for hypertension. He is being assessed regularly to see if pharmacological treatment for his dementia is required.

Remember

In all types of dementia it might be necessary to use pharmacological agents to control agitation and other behavioural disturbances, but it must be remembered that patients with Lewy body dementia are very susceptible to the side effects of anti-psychotic drugs.

Further reading

Ballard C, Gauthier S, Corbett A et al. Alzheimer's disease. *Lancet* 2011; 377: 1019–1031.

NICE (2006) Dementia: supporting people with dementia and their carers in health and social care.

http://en.wikipedia.org/wiki/Mini%20%80%93mental_state_examination

DEPRESSION

Depression is common in old age (see also p. 528). Community studies have revealed a prevalence of 11.3% for depressive symptoms and 3% for depression in the UK. Studies of elderly hospital inpatients have shown that up to 33% have depression. It is common in the elderly with chronic physical illnesses such as stroke, and it can also be the presentation of an occult physical illness such as hypothyroidism, hypercalcaemia or carcinoma of the lung. Physical illness is the biggest risk factor for depression in old age.

Remember

Whereas the clinical features of depression in old age can be the same as in younger patients, somatic complaints, delusions and decline in cognition ('pseudodementia') are more frequently noted in the elderly.

Case history

A senior nurse noted that an 83-year-old man with a CVA is not eating poorly and is losing weight. On direct questioning the patient admits to feeling depressed, and feels he has no future.

Examination showed no abnormality apart from slight residual neurological signs from his CVA.

Assessment

- Geriatric depression scale (Table 7.3) as a screening test. The Geriatric Depression Scale (shorter version) is a reliable and valid screening instrument of depression in the elderly. A score greater than 5 indicates probable depression.
- Physical examination and investigations to detect/exclude physical causes of depression, such as hypothyroidism, hypercalcaemia, malignancy. In a patient with a normal physical examination it is recommended that FBC, U&Es, LFTs, vitamin B₁₂, Ca²⁺, PO₄⁻ TFTs and chest X-ray are performed.

In this patient, these blood tests and the CXR showed no abnormality.

Remember

Always ask the patient about suicidal thoughts/intent.

Table 7.3 Geriatric Depression Scale

Choose the best answer for how you have felt over the past week:

1.	Are you basically satisfied with your life?	Yes/No
2.	Have you dropped many of your activities and interests?	Yes/No
3.	Do you feel that your life is empty?	Yes/No
4.	Do you often get bored?	Yes/No
5.	Are you in good spirits most of the time?	Yes/No
6.	Are you afraid that something bad is going to happen to you?	Yes/No
7.	Do you feel happy most of the time?	Yes/No
8.	Do you often feel helpless?	Yes/No
9.	Do you prefer to stay at home, rather than going out and doing new things?	Yes/No
10.	Do you feel you have more problems with memory than most?	Yes/No
11.	Do you think it is wonderful to be alive now?	Yes/No
12.	Do you feel pretty worthless the way you are now?	Yes/No
13.	Do you feel full of energy?	Yes/No
14.	Do you feel that your situation is hopeless?	Yes/No
15.	Do you think that most people are better off than you are?	Yes/No

The following answers count one point

A total score greater than five indicates probable depression

1.	No	9.	Yes
2.	Yes	10.	Yes
3.	Yes	11.	No
4.	Yes	12.	Yes
5.	No	13.	No
6.	Yes	14.	Yes
7.	No	15.	Yes
8.	Yes		

From Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS). *Clinical Gerontologist* 1986; **5**: 165–173.

Management

Significantly depressed patients can be treated successfully with drugs. Drugs commonly used for treating depression in older people include:

- Citalopram: a selective serotonin reuptake inhibitor (SSRI) 8–32 mg daily.
- Mirtazapine: a pre-synaptic alpha-2 antagonist is particularly useful in patients with poor appetite – 15 mg daily, increased according to response to 45 mg daily.
- Venlafaxine: a serotonin and noradrenaline reuptake inhibitor, 75–150 mg daily.

Severely depressed patients with or without suicidal ideation need urgent referral to a psychiatrist for further assessment.

- **Progress and treatment.** Management of this patient consisted of multi-disciplinary support in the community with short-term use of venlafaxine 75 mg daily to help his depression.

Further reading

Frye MA. Bipolar disorder – a focus on depression. *NEJM* 2011; **363**: 51–59.

NON-SPECIFIC PRESENTATION OF ILLNESS IN THE ELDERLY

Many illnesses in the elderly population can present in a non-specific manner. Taking a detailed and informative history can be very difficult because underlying memory loss due to dementia can be exacerbated by an acute medical problem (delirium). Information regarding the previous medical, mental, functional and social conditions is needed to make an accurate assessment of the patient's current state.

History obtained from the patient should be augmented by information from the patient's doctor, district nurse, carers, relations and neighbours, if necessary, particularly if the patient is confused.

These problems are highlighted in the following case. MEWS (Table 7.4) is a simple physiological scoring system that can be used at the bedside in a medical admission unit. It identifies patients at risk of deterioration and who may require more specialised care.

Case history (1)

Mr S. is 85 years old and lives alone in a bungalow. His neighbours noticed that he had failed to collect the milk from the front door for 2 days. They called the family doctor, who found Mr S sitting in a chair with grossly swollen feet. In his letter referring the patient to hospital the doctor confirmed that Mr S had been on salbutamol and ipratropium inhalers for 5 years. However, he hadn't visited the surgery for some time.

On arrival in hospital Mr S was very confused and unable to give a detailed history. His abbreviated mental test (AMT) score (see Table 7.1) was 3 out of 10.

On examination he had a low-grade temperature of 37.6°C, appeared breathless on minimal exertion, with central cyanosis and had signs of congestive heart failure: high JVP, an enlarged liver and leg swelling up to the groin.

A chest X-ray showed signs of left **heart failure** and there was right basal shadowing suggestive of **right lower lobe pneumonia**.

It was not clear how long he had been confused or how mobile he had been before these problems.

His next of kin was a younger brother who lived far away. He was contacted by telephone and confirmed that the patient was not married and had been able to go out to the local shops (a quarter of a mile away) until 3 weeks ago. He also commented that the patient had been mildly confused and needed some help in running his own affairs for several years, but was self-caring and didn't need help at home.

Table 7.4 Modified Early Warning Score (MEWS)

Score	3	2	1	0	1	2	3
Systolic BP (mmHg)	<70	71–80	81–100	101–199	>200		
Heart rate (bpm)	<40		41–50	51–100	101–110	111–129	130
Respiratory rate (bpm)	<9			9–14	15–20	21–29	30
Temperature (°C)	<35	34–35		35–38.4		>38.5	
AVPU score				Alert	Reacting to voice	Reacting to pain	Unresponsive

- **Treatment.** Mr S was started on antibiotics – amoxicillin 500 mg × 3 daily, bendroflumethiazide 2.5 mg daily and enalapril 2.5 mg × 2 daily for his pneumonia and heart-failure. He was also found to be hypothyroid and was started on levothyroxine 25 µg initially. His general condition gradually improved and his AMT rose to 7 out of 10.
- **Progress.** With the help of the physiotherapist Mr S was able to get back on his feet using a Zimmer frame. A home visit was successful and he went home with daily home-care support and follow-up in the day hospital, with adjustment of his medication, to maintain his mobility.

Remember

All elderly persons presenting to hospital with non-specific complaints should have full physical examinations and investigations that include FBC, U&Es, LFTs, Ca²⁺, phosphate, TFTs, ECG, MSU, CXR plus any other investigations as indicated by the findings on examination.

Case history (2)

A 79-year-old man was admitted after having had an unexplained fall. He was mildly confused but on direct questioning denied any symptoms.

On examination he had a tachycardia of 100/min, normal heart sounds and a clear chest. An ECG revealed raised ST segment in leads II, III and AVF, i.e. an acute inferior myocardial infarct (STEMI). He had a raised serum troponin.

- Any illness in old age can present with any of the so-called ‘giants’ of geriatric medicine, i.e. confusion, falls/instability and incontinence.
- In addition, some illnesses present atypically. Examples of this include:
 - ‘Silent’ myocardial infarction
 - Pneumonia without pyrexia or rise in white cell count

- ‘Silent’ peptic ulcer perforation, i.e. peptic ulcers might perforate with little or no pain but the patient becomes non-specifically unwell, anorexic and bed-bound.
- **Diagnosis.** This patient has had a ‘silent’ myocardial infarction.

Management

Aspirin 300 mg chewed with clopidogrel 300 mg oral gel were given. He was assessed urgently by the cardiac team who felt that despite his age he should be treated urgently with fibrinolytic therapy (p. 286). He responded well, with a fall in the ST segment to normal, without any complications of treatment.

- **Progress.** He was discharged and given post MI drug treatment (see below) and follow-up by the cardiac rehabilitation nurse.

Remember

Older patients often do well with active treatment of STEMI (fibrinolysis or PCI). There is no evidence to support not giving therapy to elderly patients.

APPROPRIATE ASSESSMENT SCALES

The Royal College of Physicians has produced a list of useful assessment scales/tools for the day-to-day management of the elderly. The following scales are recommended:

- **Barthel Index:** for activities of daily living (ADL) (Table 7.5).
- **Mini-Mental State Examination (MMSE):** cognitive screening test for dementia and delirium.
- **Geriatric Depression Scale:** screening instrument test for depression (see Table 7.3).
- **Waterlow Score:** for risk quantification for pressure ulcers (Table 7.6).
- **Philadelphia Geriatric Center Morale Scale:** for quality of life (Table 7.7); provides a multi-dimensional approach to assessing the psychological state of older people, i.e. well-being/life satisfaction/quality of life.

Other scales, e.g. Braden, Walsall and Maelor are also available.

The *Barthel Index* should be used as a record of what a patient does (not as a record of what the patient could do). The main aim is to establish the degree of dependence on any help, physical or verbal. A need for supervision means that the patient is not independent. Performance over the preceding 24–48 h is used when completing the Barthel Index but longer periods of assessment might be more relevant. A patient’s performance should be established using the best available evidence. Ask the patient or carer but also observe what the patient can do. The use of aids to be independent is allowed. Direct testing is not needed. Unconscious patients score ‘0’ throughout.

STROKE

This is the sudden onset of focal neurological symptoms caused by interruption of the vascular supply to the brain (ischaemic stroke) or intracerebral haemorrhage (haemorrhagic stroke).

Table 7.5 The Barthel Index

Item	Categories
Bowels	0 = incontinent (or needs to be given an enema) 1 = occasional accident (once per week) 2 = continent
Bladder	0 = incontinent/catheterised, unable to manage 1 = occasional accident (max. once every 24 h) 2 = continent (for over 7 days)
Grooming	0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Toilet use	0 = dependent 1 = needs some help but can do something alone 2 = independent (on and off, dressing, wiping)
Feeding	0 = unable 1 = needs help cutting, spreading butter, etc. 2 = independent (food provided in reach)
Transfer	0 = unable – no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility	0 = immobile 1 = wheelchair independent (includes corners) 2 = walks with help of one (verbal/physical) 3 = independent (may use any aid, e.g. stick)
Dressing	0 = dependent 1 = needs help, does about half unaided 2 = independent, includes buttons, zips, shoes
Stairs	0 = unable 1 = needs help, (verbal, physical) carrying aid 2 = independent
Bathing	0 = dependent 1 = independent (may use shower)

Table 7.6 Waterlow pressure ulcer risk assessment

Build/weight for height	Visual skin type		Continence		Mobility		Sex/Age		Appetite	
	0	1	0	1	0	1	Male	Female	Average	Poor
Average	Healthy	Tissue paper Dry	Complete	Occasionally incontinent	Fully mobile	Restricted/Difficult	1	14–18	1	2
Below average	3	Oedematous Clammy Discoloured Broken/spot	1	Catheter/incontinent of faeces	2	Restless, fidgety	2	5–64	2	3
			2	Doubly incontinent	3	Apathetic Inert/traction	3	65–75	3	4
			3		4		4	75–80	4	5
Special risk factors										
1. Poor nutrition, e.g. terminal cachexia										
2. Sensory deprivation, e.g. diabetes, paraplegia, cerebrovascular event										
3. High dose anti-inflammatory or steroids in use										
4. Smoking 10+ per day										
5. Orthopaedic surgery/fracture below waist										
Assessment value										
8										
At risk										
10										
6										
High risk										
15										
3										
Very high risk										
20										
1										
3										

The Waterlow assessment is mainly used in acute hospital settings in order to highlight patients at risk of pressure sores who will require special nursing care, including aids, and to prevent the development of pressure sores.

Table 7.7 The Philadelphia Geriatric Center Morale Scale

	High morale response	Low morale response
Do little things bother you more this year?	No	Yes
Do you sometimes worry so much that you can't sleep?	No	Yes
Are you afraid of a lot of things?	No	Yes
Do you get mad more than you used to?	No	Yes
Do you take things hard?	No	Yes
Do you get upset easily?	No	Yes
Do things keep getting worse as you get older?	No	Yes
Do you have as much pep as you had last year?	No	Yes
Do you feel that as you get older you are less useful?	No	Yes
As you get older, are things ... than you thought?	Better	Worse or same
Are you as happy now as you were when you were younger?	No	Yes
How much do you feel lonely?	Not much	A lot
Do you see enough of your friends and relatives?	Yes	No
Do you sometimes feel that life isn't worth living?	No	Yes
Do you have a lot to be sad about?	No	Yes
Is life hard much of the time?	No	Yes
How satisfied are you with your life today?	Satisfied	Not satisfied

References

Lawton MP. The Philadelphia Geriatric Center Morale Scale: a revision. *Journal of Gerontology* 1975; **30**: 85–89.

Royal College of Physicians. Report of a joint workshop with the Royal College of Physicians and the British Geriatrics Society standardised assessment scales for elderly people. RCP, 1992, London.

Case history

A 78-year-old man presents with a reduced conscious level, GCS = 12, weakness of the right arm and leg and inability to speak. His daughter thinks that he has had a stroke. She also says that her father has been well and is still working 2 days a week.

Information

Each year in England about 100 000 (1.6–2 per 1000) people have a first stroke. Stroke is the most common cause of severe disability in adult life. There are 64 000 deaths attributed to first or recurrent strokes, which makes it the third commonest cause of death in the UK.

Questions you need to address

- Is it a stroke?
- What type of stroke?
- What part of the brain is affected?
- What is the prognosis?
- Are there complications to treat or prevent?

Pathology

- 80–90% of strokes are ischaemic, i.e. due to thrombosis or embolism.
- 10–20% are the result of primary cerebral haemorrhage or aneurysm rupture.

Common sources of emboli

- Carotid artery and aortic arch atheroma
- Intracardiac sources, e.g. left atrium in AF, left ventricle mural thrombus, left-sided heart valves
- Vertebral artery atheroma or dissection.

Uncommon causes of thrombotic stroke

- Giant cell arteritis
- Other vasculitides
- Haematological disorders, e.g. polycythaemia vera, hyperviscosity syndrome.

Typical signs of a stroke

The typical signs of a stroke are listed in Table 7.8.

Features of a stroke involving the brainstem

- Hemiplegia/quadriplegia
- Ataxia/vertigo/tinnitus
- Dysphagia
- Dysarthria
- Gaze paresis

Table 7.8 Clinical deficits associated with different vascular territories of the brain

Anatomical location	Common neurological deficits
Left middle cerebral artery	Right-sided weakness involving face and arm > leg with expressive, receptive or mixed dysphasia.
Right middle cerebral artery	Left-sided weakness, face and arm > leg, visual and/or sensory neglect or inattention of left side, denial of disability (anosognosia).
Lateral medulla (posterior inferior cerebellar artery and/or parent vertebral artery)	Ipsilateral Horner's syndrome, Xth nerve palsy (due to infarction of nucleus ambiguus), facial sensory loss (trigeminal nerve), limb ataxia with contralateral spinothalamic sensory loss. Typically, patients are vertiginous and unable to feed by mouth due (mainly) to failure of laryngeal closure during swallowing and ineffective coughing. Cervical radiculopathies may occur due to involvement of radicular branches of the vertebral artery.
Posterior cerebral artery	Homonymous hemianopia with variable additional deficits due to involvement of parietal and/or temporal lobe.
Internal capsule	Motor, sensory or sensorimotor loss, involving face, arm and leg to a roughly similar extent. There may be profound dysarthria due to involvement of corticobulbar fibres but the patient should not be dysphasic or have other cortical type deficits such as dyslexia or dysgraphia.
Bilateral paramedian thalamus (30% of the population have a single common arterial stem supplying the medial aspect of both thalami)	Coma or disturbed vigilance at presentation, ophthalmoplegia (internal and/or external) ataxia and memory impairment. Some patients require ventilation.
Carotid artery dissection	Ipsilateral Horner's syndrome due to compression of the sympathetic plexus around the carotid artery; the same process can also affect the lower cranial nerves (Xth and XIIth most obvious clinically) in the carotid sheath, or the VIth nerve in the cavernous sinus. If ipsilateral cerebral infarction follows (due to hypoperfusion or embolisation) the clinical picture can mimic a brainstem event; in this way, carotid artery dissection can mimic vertebral artery dissection.

- Temperature control disturbance
- Altered respiratory pattern.

Is your diagnosis of a stroke correct?

Most strokes are easily diagnosed clinically but errors do occur. Not all acute neurological impairments are due to stroke and other conditions can be misdiagnosed as stroke.

Unusual symptoms and signs should make you question the diagnosis, e.g.:

- Papilloedema
- Persistent headache
- Fluctuating signs
- Unexplained fever
- History of trauma to head or neck.

Examples of misdiagnosis

- Todd's paresis secondary to epileptic fit
- Space-occupying lesions:
 - Primary tumours, metastases
 - Subdural haematoma
 - Cerebral abscess
- Venous sinus thrombosis
- Carotid or vertebral artery dissection
- Infections:
 - Meningitis
 - Encephalitis
- Metabolic disturbance:
 - Hypo-/hyperglycaemia
 - Hypo-/hypernatraemia
 - Renal failure
- Intoxication/overdose:
 - Alcohol
 - Drugs, e.g. sedatives, tricyclics. (*Note: focal neurological signs are common with tricyclic overdose*)
- Hypotension:
 - Hypovolaemia
 - Cardiac dysrhythmia
 - Cardiogenic shock
- Old neurological deficits, e.g. previous stroke.

Clinical problems associated with a stroke (Table 7.8)

The neurological deficit

- **Early management of a stroke**
- Thrombolytic treatment with IV alteplase (tPA) (p. 286) needs to be given in < 4½ h (ideal 90 min) of onset of stroke, haemorrhage having been excluded on scanning.
- Aspirin: 300 mg and clopidogrel 75 mg after CT scanning (to rule out haemorrhage), if fibrinolysis is not being used.
- Hydration and/or feeding: early NG or PEG (percutaneous endoscopic gastroscopy) feeding improves outcome in stroke patients who have unsafe swallowing (see below).
- Treatment of hyperglycaemia with insulin regimen initially.
- Paracetamol for pyrexia: if present.

- Prevention of complications:
 - Chest infection: attention to swallow and chest physiotherapy
 - DVT. TED stockings have been shown not to be helpful. Prophylactic low molecular weight (LMW) heparin (if haemorrhage has been ruled out) should be used early
 - Pressure ulcers
 - Contractures.
- Rapid treatment of infection (most commonly chest and urinary tract).
- Hypertension: BP often rises in acute stroke but usually settles. Lowering of BP is only necessary in the early stage for severe hypertension. Persistently raised BP requires treatment for its secondary prevention benefits (see below).
- Support and interventions for the patient and family: stroke is a major life event and both the patient and family need information and support.

Dysphagia and aspiration

Can occur in up to 50% of patients at presentation. The ability to swallow should be tested by asking the patient to swallow a teaspoon of water and *not* by putting a spatula in the throat. Some patients need further assessment by Speech And Language Therapist (SALT) and investigation by videofluoroscopy.

If the patient's conscious level is impaired, do not assess the swallow until it improves.

The condition of the skin

- Are there any pressure ulcers?
- Are there any areas of skin at risk?

Bladder function

- Incontinence can result from the neurological problem or from immobility.
- Catheterisation is required only if the patient is incontinent and there is a risk of pressure ulcers.

Remember

The specific symptoms and signs detected will depend on site of the lesion. 75% of strokes occur in middle cerebral artery territory; 15% are in the vertebrobasilar territory.

How would you investigate and treat this patient?

A CT (MR not available) scan was performed approximately 3 h after the onset of the stroke. This showed a middle cerebral artery thrombus.

The National Stroke Guidelines state that fibrinolytic therapy be commenced; fibrinolytic therapy is indicated in patients with a cerebral infarct due to a thrombus which occurred less than 4.5 hours ago (see p. 476). Therapy, however, should be given as soon as possible to allow the damaged brain to recover. CT scan in first 24 h after an infarct might appear normal; if so, it will need to be repeated if no MRI can be performed. Haemorrhage can usually be seen. An MRI scan shows an infarct early in the diagnosis.

Investigations

- FBCs
- U&Es
- Random blood glucose
- ESR
- ECG
- CXR
- CT or MRI scan of brain

Major risk factors for stroke

- Smoking
- Hypertension
- Peripheral vascular disease
- Diabetes
- AF
- Hypercholesterolaemia
- Previous stroke
- Coronary artery disease.

Remember

Poor prognostic signs in stroke are:

- Reduced conscious level on admission
- Gaze paresis
- Early and persisting urinary incontinence
- Sensory inattention
- Pre-existing disability
- Previous cognitive impairment.

Further management – rehabilitation

- Physiotherapy to maximise functional recovery and prevent contractures.
- Occupational therapy for functional assessment, aids and adaptations.
- Speech and Language Therapist (SALT) for assessment and management of speech and swallowing problems.
- Continuing medical review.

Post-stroke care and rehabilitation in stroke units has been shown to reduce mortality and early disability.

Secondary prevention after stroke

- Hypertension: persisting at 28 days after stroke should be treated according to British Hypertension Society Guidelines (p. 317).
- Anti-platelet agents: aspirin (75–150 mg daily) and clopidogrel 75 mg daily should be started. Dipyridamole MR (200 mg) is used if clopidogrel 75 mg daily is contraindicated or not tolerated.
- Anti-coagulation in patients with ischaemic stroke who make a reasonable recovery and have AF, mitral valve disease, prosthetic heart valve or within 3 months of myocardial infarction.

- Carotid endarterectomy if carotid stenosis of 70–90% is present in patients who are not severely disabled by their stroke. Early investigation and surgery should be performed within one week (p. 478).
- Statins for those with cholesterol > 3.5 mmol/L.
- Stop smoking – refer to anti-smoking clinic.
 - **Progress.** This 78-year-old man improved a few hours after the fibrolytic therapy. Two days later he was able to stand with help. With physiotherapy and speech therapy he became fully ambulant in 6 days and his speech was improving. At assessment, 3 months later, he was living an independent life.

Further reading

Hughes T. Stroke on the acute medical take. *Clin Med* 2011; 10: 68–72.

Langhorne P, Bernhardt J, Kwakkel G. Stroke Care 2. *Lancet* 2011; 377: 1693–1702.

Rothwell PM, Algra A, Amarenco P. Stroke Care 1. *Lancet* 2011; 377: 1681–1692.

www.dh.gov.uk/en/healthcare/stroke

www.rcplondon.ac.uk/stroke

HEART DISEASE IN THE ELDERLY

Case history

A 78-year-old man with long-standing atrial fibrillation was admitted with tiredness and breathlessness. He also complained of indigestion and recent falls.

Examination revealed a radial pulse of 96, apical rate 110 irregular, a raised JVP, swollen ankles and crackles up to both lung mid-zones.

He was taking digoxin 125 µg daily and aspirin 75 mg daily.

What investigations would you do?

- FBC, UE, LFTs, TFT, troponins
- ECG
- CXR.

Investigations revealed AF with no R wave progression on his ECG, suggesting a possible **acute myocardial infarct**.

His CXR showed pulmonary oedema (Fig 7.2a). The FBC showed an Hb of 98 g/L with an MCV of 70 fL, suggesting an iron deficiency anaemia, possibly related to his aspirin intake.

Learning points

- Cardiac failure in the elderly may present with non-specific symptoms such as tiredness and falls.
- Aspirin, even at low dose, can be associated with occult GI blood loss.
- Always check compliance in older people, especially if patient thinks that medication is not effective.
- Benefits have been shown for anti-coagulation of elderly patients in AF up to age 85, but contraindications (e.g. falls or gastrointestinal

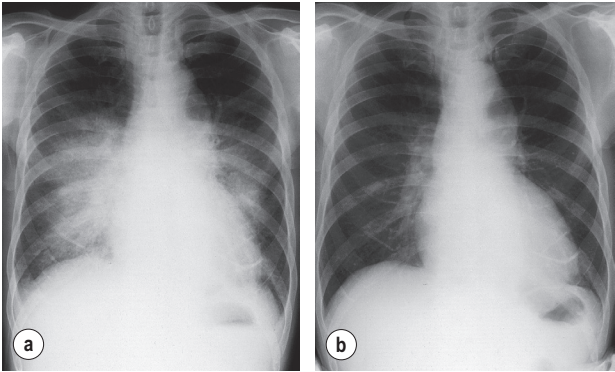


Figure 7.2 A pair of chest X-rays taken from a patient before (a) and after (b) treatment of acute pulmonary oedema. The CXR taken when the oedema was present demonstrates hilar haziness, Kerley B lines, upper lobe venous engorgement and fluid in the right horizontal interlobar fissure. These abnormalities are resolved on the film taken after successful treatment.

haemorrhage) are more common in this population. In this case the microcytic anaemia (see p. 79) would need to be investigated before starting warfarin.

- Risks of anti-coagulation in the over 85s are high and no study has shown a benefit in this age group.
- ACE inhibitors should be used in the elderly, starting with a low dose, and renal function closely monitored due to increased risk of renal impairment (p. 236).

Acute MI

The management principles of heart disease in the elderly are the same as those in young people, with a few exceptions:

Age alone is not a contraindication to thrombolysis/percutaneous coronary intervention in acute MI; in fact the greatest benefits are seen in older patients. However, other co-morbidities causing contraindications are more common in older people.

Acute MI may present silently (with no pain) more commonly in the elderly.

Treatment

He was given diuretic therapy with furosemide 40 mg orally daily. This helped his breathlessness and his ankles became less swollen. His CXR improved (Fig. 7.2b). As his presentation was over a few days he was not given fibrinolytic therapy. He was started on an ACE inhibitor with enalapril 2.5 mg.

Endoscopy was performed and he was found to have gastric and duodenal erosions due to his aspirin intake. The aspirin was stopped. Colonoscopy showed no lesion.

- **Progress.** Three weeks later he was feeling much better. He was given iron therapy. He was started on warfarin anti-coagulation.

TRANSIENT ISCHAEMIC ATTACK

This is a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without acute infarction. The arbitrary time of <24 hours is no longer used; the criteria depend on having no demonstrable lesion.

Case history

A 68-year-old man presents to the A&E with weakness of the right arm and leg, expressive dysphasia and a facial palsy. While being examined his symptoms and signs start to improve and have resolved by the time he returns from the X-ray department. A diagnosis of a transient ischaemic attack (TIA) is made.

What points do you need to ascertain in the history?

- Previous similar episodes, especially recently
- Previous episodes of amaurosis fugax (sudden transient loss of vision in one eye)
- History of palpitations, hypertension, diabetes, high cholesterol or stroke
- Smoking history
- Current and previous medication
- Functional status: mental and physical.

What are the major aspects of the examination?

- The neurological examination
- BP
- Pulse rate and rhythm
- Presence of cardiac murmurs, carotid bruits
- Papilloedema, visual field deficit, signs of retinal emboli.

Investigations

- FBC
- ESR
- U&Es
- Blood sugar
- Cholesterol
- ECG/24-h tape in selected patients
- CXR
- CT head
- Echocardiogram in patients with suspected valvular disease or mural thrombus
- Carotid duplex ultrasonography in patients with carotid territory TIAs

Should you admit this patient?

Updated National Stroke guidelines for the UK recommend that a patient with a TIA should be admitted to hospital if he/she cannot be assessed and investigated in a neurovascular clinic within 7 days of TIA.

Other reasons for admission:

- Doubt over diagnosis, e.g. need to exclude space-occupying lesion.
- Multiple TIAs in short time: these patients should also be fast-tracked to carotid endarterectomy.
- Identification of pathology requiring immediate intervention, e.g. cardiac arrhythmia.
- Background disability with poor social circumstances.

How would you manage a case of TIA?

- Aspirin 75–150 mg per day and clopidogrel 75 mg.
- Anti-coagulation with warfarin in patients with atrial fibrillation.
- Statins for those with hypercholesterolaemia (cholesterol >3.5 mmol/L).
- Treatment of risk factors, e.g. hypertension.
- Stop smoking.
- Advice not to drive for 1 month following the event.

Further management – carotid endarterectomy

(see also p. 478)

Carotid endarterectomy is recommended for patients with TIAs and minor strokes who have 70–90% stenosis of the relevant carotid artery and who are otherwise fit, with no major persisting disability.

Investigation and treatment should be performed within 1 week. MRI angiography is required prior to surgery. Carotid endarterectomy has a 1–2% perioperative stroke risk in the most experienced hands but reduces the incidence of stroke by 75% over the next 2–3 years.

The ABCD² score can help to stratify stroke risk in the first 2 days (see p. 478).

Note: asymptomatic carotid stenosis is associated with a lower stroke risk and benefit from surgery is not proven.

Prognosis after untreated TIA over 4 years

- 25% dead
- 25% stroke
- 10% MI.
- *Progress.* This man had a carotid endarterectomy performed 6 days after his admission to hospital. He made a good recovery and at review at 6 months he was still taking treatment for stroke prevention and had started on an exercise programme.

HYPOTHERMIA

Information

Hypothermia is defined as core body temperature of < 35°C. It is associated with many clinical conditions and in most patients aetiology is multifactorial.

Case history

An 89-year-old female is found lying on the floor by her carer. On arrival at the A&E department she is noted to be confused and have a rectal temperature of 34°C.

Aetiological factors

- Exposure to cold
- Impaired thermoregulation
- Impaired shivering thermogenesis
- Low metabolic heat production
- Impaired temperature perception
- Drugs, e.g. phenothiazines, hypnotics, alcohol
- Hypothyroidism
- Intercurrent illness.

Clinical features

These vary with the degree of hypothermia. Whereas those with a core temperature of 33–34°C can be confused and have slow cerebation, those with a temperature of 30°C are more likely to be drowsy and have muscular stiffness.

Some patients with hypothermia have features such as slow relaxing reflexes, which are suggestive of hypothyroidism.

The electrocardiograph can show changes such as sinus bradycardia, slow AF, prolonged PR interval, 'J' waves (commonly seen in leads V3-V4) (Fig. 7.3).

Complications of hypothermia include pancreatitis, oliguria, cardiac arrhythmias (particularly during re-warming) and aspiration pneumonia.

Investigations

- FBC
- U&Es
- Glucose
- Amylase
- LFTs
- Calcium
- Arterial blood gases
- ECG
- CXR
- Thyroid function tests

This patient was found to be grossly hypothyroid with a TSH of 14.3 mU/L and a T4 of 4 pmol/L.

How would you manage this patient?

This patient was managed as follows:

- Nursed with space blanket in a warm room (allow temperature to rise by 0.5°C/h).

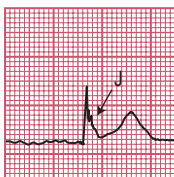


Figure 7.3 ECG showing J waves.

- Oxygen: remember that patients with COPD might require 24% oxygen.
- IV fluids (through blood warmer).
- Her severe hypothyroidism was treated with triiodothyronine 5–10 μg slowly IV 12-hourly.

A severely hypothermic patient will require admission to ITU and require positive pressure ventilation, CVP line, and ECG monitoring may be necessary.

- **Progress.** This woman made a slow but steady recovery and was discharged home on levothyroxine 125 μg daily with a follow-up appointment.

Further reading

Mallet ML. Pathophysiology of accidental hypothermia. *Quarterly Journal of Medicine* 2002; **95**: 775–785.

PRESSURE ULCERS

Pressure ulcers are common. Ill elderly people are most at risk of developing pressure ulcers. The reported prevalence rates vary widely – on average 5–10% of this group.

Case history

A 78-year-old woman with a right hemiplegia from a previous stroke was brought to A&E having fallen at home. She had been on the floor for at least 24 h because she was unable to get up.

On examination she was conscious and aware of her surroundings. There were no specific abnormalities on physical examination, apart from evidence of a right hemiparesis. When examining her you notice a dusky area over the right hip overlying the greater trochanter.

Risk factors for developing pressure ulcers

- Low body weight/excessive body weight
- Poor nutritional state
- Motor deficit/immobility
- Sensory deficit
- Presence of intercurrent illness
- Incontinence: bladder/bowel
- Use of certain medication, e.g. long-term prednisolone, sedatives and analgesics, which reduce sensation and hence stimulation to move.

Other patients at special risk

- Undergoing surgery particularly orthopaedic surgery
- With neurological disease
- With spinal cord injury including cord compression
- Having palliative care.

Why do pressure ulcers occur?

Pressure greater than the mean capillary pressure (25–32 mmHg) will occlude blood vessels and lead to anoxia of the skin. Hard surfaces can generate pressures greater than 100 mmHg, therefore the damage to the skin results from the pressure applied and the length of time exposed to the pressure. In addition to pressure, shearing force is another significant factor.

Pressure ulcers can be graded into superficial (grades 1 and 2) and deep (grades 3 and 4).

Clinical assessment

Document pressure ulcers fully:

- The site, size and grade of pressure ulcer
- The condition of the surrounding skin
- The presence/absence of infection
- Photography is a good method of recording pressure ulcers and monitoring change.

General examination of the patient with special regard to:

- Nutritional state including body weight
- Full neurological examination
- Abdominal examination, especially bladder and bowel.

How would you investigate?

Investigations will be directed by the physical examination, but special attention should be paid to those in the Investigations box.

Investigations

- FBC: presence of anaemia will delay wound healing
- Albumin: marker of nutrition, low albumin will delay wound healing
- Blood sugar: hyperglycaemia delays healing
- Wound swabs for culture and sensitivity
- Blood cultures if concern about septicaemia
- If the wound is deep, overlies a bony prominence and has been present for some time, X-ray of the underlying bone should be performed to rule out osteomyelitis

How would you manage pressure ulcers?

Prevention is definitely better than cure and all at-risk patients require immediate assessment.

Remember

- Pressure ulcers can develop in 1–2 h
- Beware of leaving patients on hard A&E trolleys or X-ray tables for too long.

- Relief of pressure with appropriate support mattress and/or cushion for chair:
 - Low-risk patients: a soft overlay to the mattress may be adequate
 - High-risk patients: an alternating pressure support system, e.g. special pressure-relieving mattresses.
- Appropriate dressings for wounds. *Note:* dry dressings should not be used on moist wounds. Examples of dressings include:
 - Hydrocolloid for superficial granulating wounds
 - Alginates for exuding or bleeding wounds.
- Treatment of infection (cellulitis or associated septicaemia) when present, with appropriate systemic antibiotics.
- General management of the patient:
 - Pain relief
 - Treatment of medical conditions, including anaemia
 - Review of drug treatment: NSAIDs and steroids delay wound healing
 - Review of nutrition: including use of supplements, including vitamin C and zinc
 - Management of incontinence.
- Severe pressure ulcers often require surgical debridement and skin grafting by plastic surgeons, when non-infected.

Most hospitals have tissue viability specialist nurses to advise on prevention and treatment of pressure ulcers. For quantification of risk, these nurses can use the Waterlow score or Norton Scale (see p. 165).

- **Progress.** This patient was admitted to MAU and the tissue viability nurse was contacted to assess her pressure areas. However, despite immediate treatment she developed a pressure ulcer over her right hip.

Further reading

National Institute for Clinical Excellence (NICE) 2001 Pressure ulcer risk assessment and prevention. NICE, London.

Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers; a systematic review. *JAMA* 2006; **296**: 974–984.

URINARY TRACT INFECTION AND INCONTINENCE

Case history

An 80-year-old woman with mild dementia presented with 24 h of increasing confusion and drowsiness. She had a 3-day history of urinary incontinence and diarrhoea. She was taking co-dydramol for arthritis.

Continued

Case history (continued)

Examination revealed a woman with confusion, with no knowledge of her surroundings or time of day. Her GCS score was 12. Examination of her abdomen was normal but rectal examination showed constipation with faecal impaction and overflow diarrhoea. A urine sample was offensive, and positive to Stix testing for nitrites, leucocytes, blood and protein.

Particular points to note in the history

- Urinary tract infection in the elderly can present with non-specific symptoms such as confusion, drowsiness or falls.
- Recurrent UTIs should be investigated (> 3 in a woman, > 1 in a man) with renal tract ultrasound, including assessment of post-micturition bladder volume.
- New urge incontinence may be precipitated by infection leading to an unstable bladder.
- Infection can be precipitated by obstruction: most commonly caused by constipation or prostatic hypertrophy.
- Drug history for precipitating causes: drugs causing constipation, diuretics, sedatives.

Examination of this patient included:

- Full physical examination for coexisting causes of confusion, e.g. chest infection.
- Rectal examination – to assess for constipation/overflow (prostatic enlargement in men).
- Neurological examination to exclude neurological causes of urinary retention and constipation.

Investigations

- Stix testing positive for both leucocytes and nitrites is highly specific and sensitive for infection: blood and protein Stix are much less useful. *Note:* bacteriuria without symptoms (urgency, frequency, dysuria or systemic symptoms) is common in hospitalised/institutionalised older people and should not be treated, even if bacterial count is $> 10^5$
- In-out catheterisation can be useful for obtaining specimens or assessing residual volumes. However, catheterisation should not be used as a treatment for incontinence
- FBC
- Blood cultures
- U&Es
- Creatinine (eGFR)
- AXR for evidence of constipation
- Consider further assessment of incontinence if it doesn't settle on treatment of infection

How would you treat this patient?

- Treat infection with oral antibiotics.
 - Trimethoprim 200 mg × 2 for 3–5 days is a good first line treatment. Only use parenteral antibiotics if the patient is very ill or vomiting.
- Treat constipation: enemas and laxatives (see p. 36). Stop co-dydramol. Repeat residual volumes after constipation is treated as this patient's constipation was likely to be due to the codeine in co-dydramol. The latter was replaced by paracetamol.
 - **Progress.** This patient's confusion and drowsiness improved with successful treatment of her UTI. Her faecal impaction was relieved by the enemas but she is still inclined to constipation and this is treated symptomatically with Magrols.

Further reading

Elements of provisional discharge plan. *Clinical Medicine* 2011, 80.

ARTERITIS

Case history

An 82-year-old widower was admitted with left-sided temporal headache of 3 days' duration. He is known to have Type 2 diabetes (on insulin), visual impairment due to macular degeneration, hypertension and an old left hemiparesis. He lives alone in a house and has one son who lives far away.

Medical assessment

On examination he had signs of an old left hemiparesis and a peripheral neuropathy (probably due to longstanding diabetes) and visual impairment. His BP was 150/80 on losartan therapy. In addition, it was noted that the left temporal artery was pulsatile but tender.

Investigations revealed a significantly elevated ESR (> 100 mm in 1 h).

A clinical diagnosis of **temporal arteritis** (see p. 212) was made. His response to steroids was very good, although he remained tired and slightly more frail than previously

How would you organise his discharge?

The patient needs a multidisciplinary assessment before his discharge to ensure his safety. His son should also be contacted, with the patient's permission.

General points for discharge planning

Discharge planning of an elderly person should start as early as possible after admission. Once the person's medical problems have been accurately diagnosed and treated, his/her potential for returning home should be assessed by a multidisciplinary team (MDT) of professionals, taking into account the elderly person's views.

Remember

A competent adult has a right to decide whether he or she wishes to go home, even if this decision is against the advice offered by member(s) of the multidisciplinary team (MDT).

The assessment by MDT includes:

- Assessment by a physiotherapist to assess his/her mobility, transfers and ability to climb stairs.
- Assessment by an occupational therapist to assess independence and safety in activities of daily living, kitchen assessment and/or a home visit.
- Social work assessment that will take into account the assessments of other professionals to quantify his/her needs for care on discharge.
- Assessment by a speech and language therapist, dietitian or a psychologist in some cases.
- Referral to a district nurse, e.g. for treatment of leg ulcers, monitoring of diabetic control, monitoring of medication.
- Discussion with GP about on-going medical care.

Following discharge it might be possible to continue further rehabilitation or monitoring of medical or nursing care in a day-hospital setting.

- **Progress.** This patient was keen to go home, even though he was still frail. He required full support at home with community nurses managing his insulin therapy. His headaches disappeared on his steroid therapy which was reduced, making his diabetes easier to manage. He continues to improve.

ACUTE HOT JOINT

Case history

An 80-year-old man presents with a hot, painful, swollen knee joint. He takes a thiazide diuretic for hypertension and has recently had a chest infection treated by his GP.

What are the possible causes?

- Acute gout (see p. 209).
- Acute pseudo-gout (pyrophosphate arthropathy) (see p. 211).
- Septic arthritis (see p. 219)
- Acute flare-up of chronic arthritis, e.g. rheumatoid arthritis (RA; see p. 200).
- Traumatic haemarthrosis with fracture of patella or tibial plateau
- Ruptured Baker's cyst in osteoarthritis (see p. 191).

Particular points you should elicit in the history

- Trauma or injury: entry for infection
- Drug history: particularly diuretic
- Known arthritis or previous episodes, e.g. of gout
- History of intercurrent illness.

On examination you should look for:

- Temperature, pulse: systemic signs of infection/inflammation
 - Joint colour, temperature and tenderness
 - Evidence of trauma
 - Other joint disease, including evidence of RA or osteoarthritis (OA).
- Joint fluid should be sent for culture, cell count and examination under polarised light. Urate crystals are distinguished by being negatively birefringent. Calcium pyrophosphate consists of weakly positively birefringent rhomboidal crystals.

Investigations

- X-ray joint
- Tap joint under sterile conditions: fluid for culture, crystal detection and cell count
- Blood cultures
- FBC for WCC and ESR
- Serum uric acid
- Rheumatoid factor, CCP and autoantibody screen if appropriate

How would you manage this patient?

This patient's serum uric acid is in the high range 700 $\mu\text{mol/L}$ which is compatible with gout.

His joint aspiration showed a cloudy viscous fluid containing 4020 WCC/ mm^3 and negative birefringent needle shaped crystals.

- **Diagnosis.** Gout.

Treatment

There are three acute options:

- An NSAID: e.g. ibuprofen 400 mg \times 3 daily or diclofenac with misoprostol one tablet \times 3 daily (Misoprostol is a cytoprotective agent to the gastric mucosa).
- Colchicine (rarely used only because it causes diarrhoea): 1 mg initially, 0.5 mg every 2 h until attack subsides or 0.5 mg \times 2 daily for 5 days if symptoms are not severe.
- Intra-articular corticosteroids: injection with methylprednisolone 40 mg with 1 mL of 1% lidocaine.

Allopurinol **should not** be used acutely. *Prophylactically*, it is started at least 4 weeks after the acute attack has settled to prevent further attacks of gout.

- **Progress.** This man's knee became less painful and the swelling settled after 1 week's NSAID therapy. His thiazide diuretic was stopped and replaced with losartan. He has had no further attacks of gout.

Further reading

Neogi T. Gout. *NEJM* 2011; **364**: 443–452.

PARKINSON'S DISEASE

Case history

An 80-year-old man with a history of hypertension presents with a fall. He has had numerous falls recently and on questioning said he had slowed down generally.

You notice immediately a tremor in his left arm, lack of facial expression and a monotonous voice. The diagnosis is **Parkinson's disease (PD)**.

Features of PD

- Akinesia/bradykinesia:
 - Poor initiation of movement
 - Slowing of repetitive movements
 - Fatigue.
- Rigidity:
 - Lead pipe
 - And/or cogwheel (if tremor is present).
- Tremor: 70% of patients present with tremor, usually unilateral:
 - Rest tremor
 - 3–7 Hz
 - Absent in 30% at presentation.
- Postural instability is usually a late feature of idiopathic PD.
- Response to L-dopa suggests idiopathic PD.

Remember

- The disease is often asymmetrical at presentation
- Depression is a common association, often missed.

Clinical diagnosis of PD

PD is a clinical diagnosis; there are no diagnostic tests. Diagnosis requires two cardinal features, including:

- Akinesia/bradykinesia of the upper body
- Asymmetrical onset with resting tremor
- Clear response to levodopa.

What is the differential diagnosis of PD?

- Essential tremor:
 - Isolated tremor, can affect the head (Yes/Yes or No/No pattern)
 - Becomes more prominent with increasing age
 - Autosomal dominant inheritance
 - Responds to alcohol, beta blockers.
- Arteriosclerotic parkinsonism:
 - History of cerebrovascular disease and hypertension common
 - Wide-based, short stepped gait: *marche à petit pas*
 - Upper part of body not affected
 - Limited/transient response to L-dopa.

- Drug-induced parkinsonism:
 - Anti-psychotic drugs, especially depot preparations
 - Metoclopramide: acute.
- Rarer causes of parkinsonism:
 - Multiple system atrophy, Shy-Drager parkinsonism: autonomic failure and dementia
 - Steele-Richardson-Olszewski parkinsonism: with loss of voluntary conjugate deviation of gaze, and pseudobulbar dysarthria.

Remember

You must question a diagnosis of PD if there is:

- Poor response to L-dopa
- Early instability
- Pyramidal or cerebellar signs
- Early autonomic failure, e.g. postural hypotension, incontinence
- Dementia early in course of disease
- Voluntary downward gaze palsy.

How would you manage this patient?

- This patient was started on L-dopa as first-line treatment (e.g. Co-beneldopa 62.5 mg \times 2 daily) as it is useful in the elderly. Dose requires titration depending on improvement and side effects of medication, e.g. postural hypotension, nausea, hallucinations.
- Synthetic dopamine agonists (Ropinirole, Pramipexole) are less effective but might be useful in early disease. Hallucinations and somnolence are common side effects but they are tolerated by approximately 46% of very elderly patients. They may need to be used with domperidone to avoid gastrointestinal side effects. Other dopamine agonists have ergot side effects and are poorly tolerated by the elderly.
- Monoamine oxidase inhibitor (MAOI-B): selegiline – avoid in patients with postural hypotension or hallucinations.
- Catechol-O-methyl transferase inhibitor (COMT) inhibitors (e.g. tolcapone, entacapone) are used as adjuncts to L-dopa.
- Apomorphine SC infusion is used in specialist centres.
- The frequency of his falls improved with PD therapy but nevertheless, exercise and balance training was started. He was referred to an MDT to assess need for walking aids and changes in the home environment.
 - **Progress.** The patient was commenced on Co-beneldopa 62.5 mg \times 2 daily and was able to return home with community support.

Further reading

Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet* 2009; **373**: 2055–2066.

DRUG TREATMENT IN OLDER PEOPLE/DRUG TREATMENT AS A CAUSE OF ILLNESS AND ADMISSION TO HOSPITAL

Individuals over the age of 65 make up approximately 18% of the population but represent 25–30% of drug expenditure. Approximately 87% of the elderly take one prescribed medication and one-third of this group take three or more drugs.

Age-associated increases in the incidence of adverse reactions have been well described for certain groups of drugs, e.g. benzodiazepines.

The most frequently used classes are cardiovascular drugs, analgesics, gastrointestinal preparations and sedatives (Table 7.9).

DRUGS AS A CAUSE OF ILLNESS AND DELAYED DISCHARGE

Table 7.9 Drugs that are more likely to produce adverse effects in the elderly

Drug	Adverse effects
Benzodiazepines	Sedation, drowsiness, confusion, ataxia
Non-steroidal anti-inflammatory drugs	Gastric erosions, fluid retention, renal impairment and drug interaction, e.g. diuretics
Opiates	Sedation, confusion, constipation
Antimuscarinic	Urinary retention, glaucoma
Antiarrhythmics	Confusion, urinary retention, thyroid problems
Antipsychotics	Confusion, sedation, tardive dyskinesia, malignant hyperthermia
Diuretics	Dehydration, hyponatraemia, hypo- or hyperkalaemia, postural hypotension, renal impairment, gout
Antibiotics	Renal failure, diarrhoea, auditory complications

Case history (1)

A 75-year-old woman was admitted to MAU with a severe cough and purulent sputum. She was known to have COPD and this was thought to be an infective exacerbation.

On examination she was tachypnoeic but not cyanosed.

Examination of her chest showed diffuse wheeze with some basal crackles. Her oxygen saturation was 92%.

She was started on amoxicillin 500 mg \times 3 a day, and erythromycin 500 mg \times 4 a day, in addition to nebulised salbutamol and ipratropium, with a good response.

A few days later she developed watery diarrhoea, which was bad enough to require IV fluids. Her stool analysis was positive for

Case history (1) (continued)

Clostridium difficile toxin (see p. 9). She was prescribed a 10-day course of metronidazole 400 mg \times 3 a day. Apart from transient nausea, she made a good recovery from her diarrhoea and was able to go home after 6 days.

Case history (2)

A 71-year-old woman was admitted with malaise, fatigue, weight loss and generally feeling unwell.

On examination she looked anxious, underweight and tremulous with a tachycardia.

In the past she had suffered from atrial fibrillation and was taking amiodarone 200 mg once daily.

Investigations revealed thyrotoxicosis (thought to be due to amiodarone) with undetectable TSH $<$ 0.05 mU/L and very high free T3 10 pmol/L and T4 35 pmol/L.

The amiodarone was stopped and her cardiologist contacted about alternative therapy for her AF (p. 275). She was started on anti-thyroid therapy (carbimazole 10 mg \times 3 daily) and steroids (prednisolone 40 mg once daily). Her response was slow and she remained an inpatient for 2 weeks before her condition was brought under control. She was seen in the Endocrine Clinic for dose adjustment of her carbimazole.

Case history (3)

A 79-year-old woman with a background of Type 2 diabetes and ischaemic heart disease was admitted to MAU with uncontrolled diabetes and progressive shortness of breath. She was taking gliclazide 160 mg \times 2 a day and co-amilofruse (5 mg amiloride, 40 mg furosemide) one tablet in the morning. A few weeks prior to admission she complained of back pain and her doctor prescribed diclofenac 50 mg \times 3 a day (an NSAID).

On examination she was in acute left ventricular failure with a tachycardia, raised venous pressure, gallop rhythm and basal crackles. She was treated acutely with oxygen, IV furosemide 50 mg and buccal glyceryl trinitrate 2 mg repeated every 20 minutes. There was no evidence of an acute ischaemic episode or chest infection.

- **Progress.** The NSAID was stopped. The dose of furosemide was doubled to 80 mg daily with 2.5 mg of amiloride. Her symptoms settled gradually over the next few days and her furosemide was then reduced without recurrence of her LVF. Her diabetes is well-controlled on gliclazide with a HbA1c of 6.5% (48 mmol/mol).

Remember

NSAIDs cause fluid retention, and can precipitate heart failure in susceptible individuals (e.g. patients with diabetes, hypertension or renal failure).

DO NOT ATTEMPT RESUSCITATION (DNAR) DECISION-MAKING

Case history (1)

A fit, elderly, 72-year-old man presents with an acute myocardial infarct. If he has a cardiac arrest would you resuscitate him?

Case history (2)

A 75-year-old woman presents with hypercalcaemia secondary to disseminated lung carcinoma. You treat her hypercalcaemia aggressively. A nurse asks whether the patient should be recorded for resuscitation or not.

What would you say?

Cardiopulmonary resuscitation (CPR) is an everyday practice in most hospitals. Despite the success in selected patients there is a consensus that CPR might be inappropriate (e.g. in terminal illness) or ineffective (e.g. very severe pneumonia) in some patients. Age alone is not a contraindication to CPR.

All decisions should be made by senior medical staff after discussion with a patient (if competent), other members of the team and family/carers (if patient lacks mental capacity).

What principles might guide you to decide to withhold CPR?

- Likely effectiveness of CPR: only 6–15% of patients who undergo CPR leave hospital alive. A number of factors predict a poor outcome from CPR attempts. These include:
 - Pneumonia
 - Chronic kidney disease
 - Anaemia (< 90 g/L)
 - A high level of dependency including housebound lifestyle
 - More than two acute medical conditions.
- Patient's wishes: these can be ascertained in advance or from advance directives and living wills. Mentally competent patients who express their wishes on treatment, including CPR, must have those wishes respected. The guidance also recommends that a patient can refuse to accept a DNAR (do not attempt resuscitation) order made by a clinician

and that, under the Human Rights Act (in HR), doctors must respect this decision and record the change. However, if a patient is not mentally competent to decide whether to accept CPR, the doctor must consult family/carers and/or the family doctor to ascertain what the patient's wishes would have been. He/she then uses this information to 'act in the patient's best interest'. *Note:* there is no provision in law in England and Wales for relatives to make medical decisions, including CPR, on behalf of an adult.

- **Quality of life:** this is the most difficult aspect to address. It includes quality of life as it is now and also after a CPR attempt, which might be worse. Difficulties arise because it involves professionals making value judgements about other people's lives.

Remember

- If no DNAR decision is documented: the patient is for resuscitation
 - Any DNAR decision made should be communicated to all members of the healthcare team involved with the patient
 - DNAR decisions should be reviewed if appropriate (i.e. not necessarily in terminal illness).
-
- **Case 1.** This man should be resuscitated. Many patients recover from a myocardial infarction, even if elderly.
 - **Case 2.** This woman should have a DNAR note in her clinical records as she is suffering from disseminated cancer.

Further reading

www.resus.org.uk

General further reading

www.bgs.org.uk. British Geriatric Society.

www.effectiveolderpeoplecare.org. Cochrane evidence for best practice in the care of frail elderly people.

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OSTEOARTHRITIS (OA)

Case history

A 75-year-old woman attends the A&E department with pain in the left groin. The pain has been present for several months but she has not sought medical advice until now. The pain is now so severe that she is unable to walk more than a few yards and it is keeping her awake at night. She lives alone and is unable to manage either her pain or to cope alone at home.

On examination movements at the left hip were decreased compared to the right and movement was painful, compatible with OA of the hip.

The SHO in A&E has arranged for a pelvis X-ray, which shows OA of the left hip. You are asked to see her for possible admission.

Describe the main radiological features of OA of the hip

The radiograph shows joint space narrowing, periarticular sclerosis, cyst formation and osteophytes. These are the four classic features of osteoarthritis (Fig. 8.1).

How would you assess this patient?

The long-standing history suggests a gradual onset of the pain. A short history or systemic symptoms might have indicated joint sepsis or a pathological fracture.

The main site of the pain – especially in the left groin radiating into the left thigh/knee – indicates that the hip is the source of the pain. Beware referred pain either from the lumbar spine (common) or the knee (less common).

A full musculoskeletal examination is needed. The GALS (Gait, Arms, Leg, Spine) is a useful screen (Doherty et al., 1992) (Fig. 8.2).

Diagnostic clues

Look for Heberden's (distal interphalangeal joints)/Bouchard's (proximal) nodes, 'square' hands, painful thumb, carpometacarpal joints that indicate primary nodal OA. Figure 8.3 shows the distributions of generalised OA and pyrophosphate arthropathy.

Examine

- Other joints for evidence of inflammatory arthritis, e.g. psoriatic arthritis, rheumatoid arthritis (RA).



Figure 8.1 Severe osteoarthritis of the hip.



Watch the patient walk away and then turn back towards you

Figure 8.2 Musculoskeletal examination: gait, arms, leg, spine.

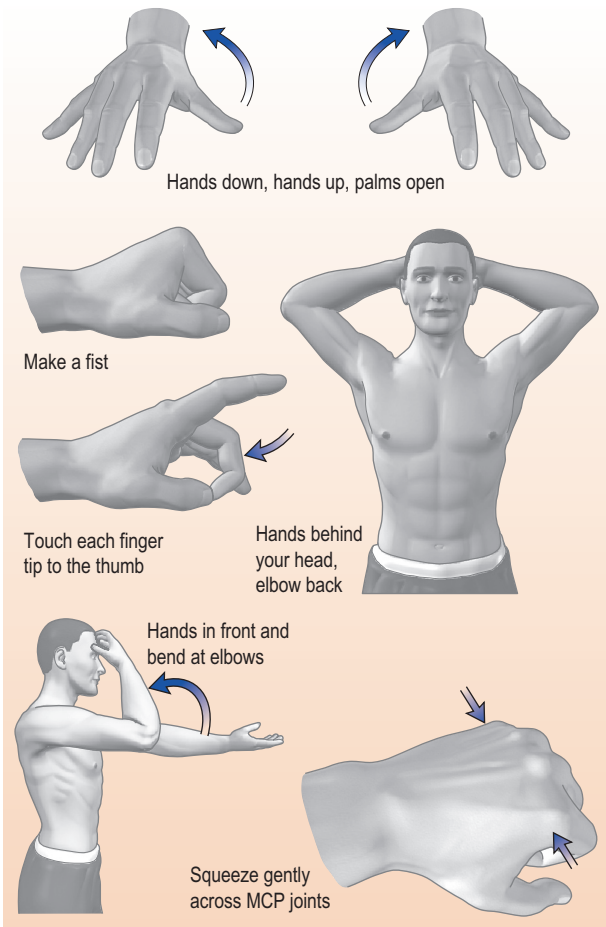


Figure 8.2, cont'd

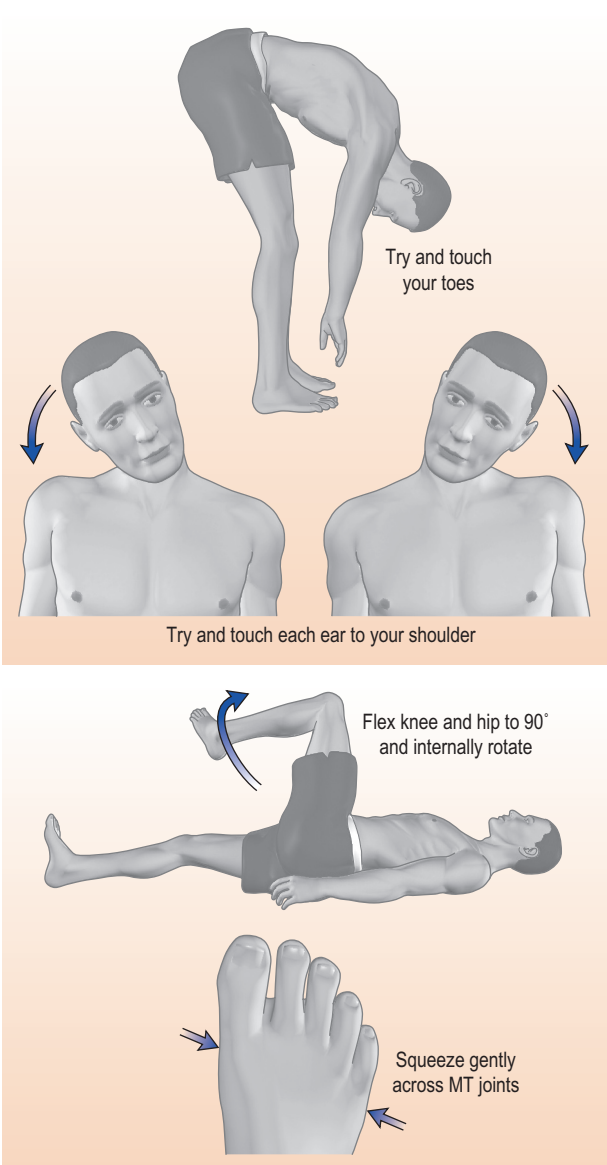


Figure 8.2, cont'd

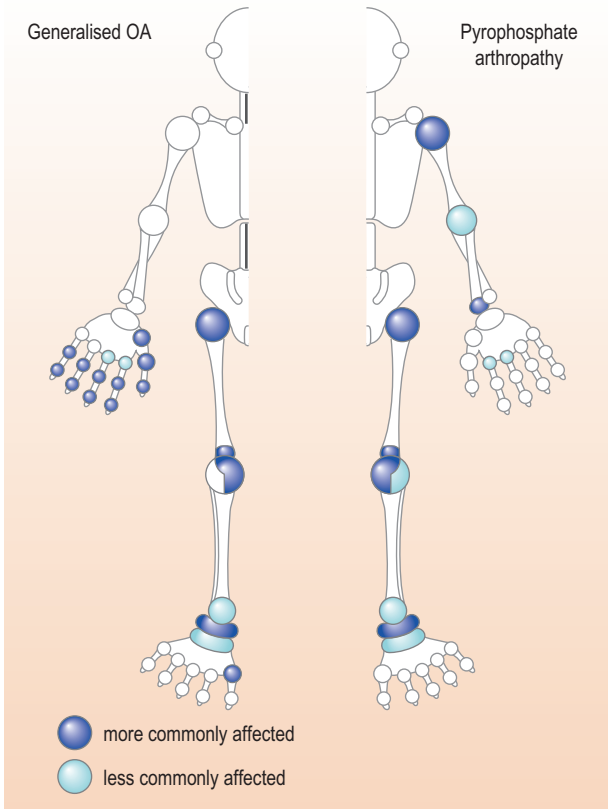


Figure 8.3 Generalised nodal OA and pyrophosphate arthropathy.

- Lumbar spine for referred pain.
- Hips:
 - Ask patient to walk to assess gait
 - Measure leg lengths
 - Assess range of all movements fully and compare with right hip. Examine from behind to look for pelvic tilt and perform Trendelenburg's test.

What points would you consider when deciding if admission is appropriate?

Full general medical examination is essential because co-morbid conditions in this age group are common. For example, in a patient with

significant disability, consider the possibilities of pneumonia, cardiac disease or urinary tract infection. The patient's nutrition might be poor, raising the possibility of osteomalacia – a well-described problem in the elderly.

A full assessment of the patient's ability to cope is essential and you should ask her about her ability to wash, dress and feed herself. This disability assessment will weigh strongly when discussing admission to hospital.

Initial treatment

- Admit because:
 - The patient lives alone
 - She needs pain control
 - Considerably disabled.
- Analgesia: simple or compound analgesia as first-line therapy, e.g. paracetamol up to 4 g/day. If this fails, a short course of an NSAID, e.g. Diclofenac usually helps the pain. There is a high risk of GI toxicity with long-term NSAID use in her age group. A gastro-cytoprotective agent, e.g. omeprazole, should be co-prescribed. Opiates should be avoided unless other analgesia has not worked because of sedation/confusion and constipation.

Investigations

- FBC
 - CRP or ESR
- NB. If she had been febrile, blood cultures must be taken

Later management

Refer to rheumatologist or medicine for the elderly consultant. In the meantime, organise:

- Physiotherapy:
 - Mobilise hip, joint protection exercises
 - Assess walking aids, e.g. stick, Zimmer frame
 - Consider hydrotherapy.
- Occupational therapy and social work assessments.

There should be detailed planning before discharge, including liaison with the doctor and a home visit.

Indications for surgery

Referral to orthopaedics for surgery:

- Severe pain especially night pain
- Poor mobility.
 - **Progress.** The general health of the patient was good and hip surgery is a very effective treatment. She therefore underwent a total hip replacement (THR). The postoperative recovery was excellent and she was able to walk without pain.

Further reading

Doherty M, Dacre J, Dieppe P, Snaith M. The GALS Locomotor Screen. *Annals of Rheumatological Disease* 1992; **51**: 1165.

RHEUMATOID ARTHRITIS (RA)

Case history

A 26-year-old woman presents at A&E with sudden onset of severe, widespread joint pain and swelling affecting her hands, wrists and feet symmetrically. She has lost half a stone in weight and feels systemically unwell.

On examination you find that she has hot joints with a symmetrical synovitis, joint restriction of the wrists, MCP and PIP joints and painful MTP joints. You suspect this is an acute onset of RA.

What other conditions could give a similar clinical picture?

- Systemic lupus erythematosus (SLE)
- Erythrovirus B₁₉ infection
- Post-streptococcal arthritis
- Psoriatic arthritis
- Primary Sjögren's syndrome
- Some systemic vasculitides.

In the first two differential diagnoses there are often other features. In SLE photosensitive rashes, hair loss, serositis and oral ulceration are seen. Erythrovirus B₁₉ nearly always presents with flu-like symptoms and a widespread rash.

Post-streptococcal arthritis may be preceded by a sore throat but is rare. Psoriatic arthritis is usually asymmetrical but can occasionally present with a symmetrical pattern. Psoriatic nail changes and other evidence of psoriasis are usually present, although these might develop after the onset of arthritis.

Sjögren's syndrome can be associated with intermittent parotid swelling and sicca symptoms: dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).

How would you manage this patient?

Remember

Rheumatoid arthritis is a multisystem disease so look carefully for pulmonary, cardiac or neurological involvement, although these are less common at presentation.

A full history and general medical examination is essential. Specific points:

- Look for nodules or vasculitis: uncommon at first presentation.
- A full musculoskeletal examination noting the symmetry of the joint involvement.

- Look for persistent inflammatory symmetrical arthritis (PISA). The most common cause of this is rheumatoid arthritis.

The most commonly involved joints at onset in rheumatoid arthritis are: wrists, MCPs, PIPs and MTP joints.

Admission is necessary if the patient is very unwell systemically and to exclude other pathology.

Investigations

- FBC/ESR, biochemistry including globulin level, CRP (the finding of a high ESR but normal CRP is characteristic of SLE)
- ANA/rheumatoid factor
- Anti CCP is positive early in the disease
- X-ray hands and feet for erosions, periarticular osteopenia (Fig. 8.4) (MRI if necessary)
- ASO titre if sore throat
- Blood cultures if febrile
- Erythrovirus B₁₉ titres if the ANA/RhF are negative

Initial management

- A short period of bed rest, ice packs if only a few joints involved.
- NSAIDs: ibuprofen is the safest; other NSAIDs have a higher risk of GI toxicity, although this patient is young.
- Disease-modifying anti-rheumatic drugs (DMARDs): these should be given at the earliest opportunity because RA is a systemic disease that



Figure 8.4 X-ray of early RA showing typical erosions at the thumb and middle MCP joints and at the ulnar styloid (arrows).

leads rapidly to joint damage and disability. It is no longer acceptable to treat RA with NSAIDs alone. There is accumulating evidence to show that early DMARD use delays joint damage and functional disability. Initial DMARDs commonly used include sulfasalazine, methotrexate or azathioprine. Others, such as IM gold and D-penicillamine, are less commonly used but still effective. Hydroxychloroquine and auranofin are the least effective but can be used in combination regimens. Combination therapies are showing good results.

Anti-TNF α agents, e.g. infliximab and etanercept, are effective when initial DMARD therapy has failed. Infectious complications such as tuberculosis are a concern with these agents.

Late manifestations of RA

Changes in the hand are shown in Figure 8.5. Other joints such as knees and hips become involved later in the disease course.

Ulnar deviation



A

Boutonnière deformity



Swan-neck deformity



B

Figure 8.5 Rheumatoid arthritis (RA) – late manifestations.

All drugs need careful explanation to the patient and close monitoring for toxicity.

Prednisolone is not used in young patients but intramuscular methyl prednisolone 40–120 mg gives excellent short-term benefit.

The addition of prednisolone 7.5 mg to existing DMARD therapy might retard the progression of erosions, but studies in this area remain controversial and this is not recommended for general use at present.

- **Diagnosis.** This patient had a high ESR of 60 mm/h and a CRP of 90 mg/L, suggesting active disease. Her anti-CCP antibodies and rheumatoid factor were positive in the serum, typical of rheumatoid arthritis. The X-rays of her hands showed only soft tissue swelling. An MRI was therefore performed and showed early erosions, confirming the diagnosis.
- **Progress.** This patient was admitted and symptomatically treated with analgesics. She was started on prednisolone and methotrexate. The pain and swelling improved and she was discharged with still some remaining residual problems. She was given a follow-up in clinic for 2 weeks.

SLE AND VASCULITIS

Case history

A 28-year-old woman is referred to you by her doctor. Six weeks ago she delivered her first baby and the pregnancy and delivery were uneventful. Two weeks after delivery she developed a widespread polyarthritis affecting her hands, feet and knees and a photosensitive rash on her face. In the last week or two she has become extremely unwell with weight loss and painful lesions on her hands and feet.

On examination she is clearly unwell with a facial rash and severe oral ulceration. Examination of her hands and feet shows extensive digital infarcts with necrotic ulceration on the palms, finger pulps and soles of the feet. There are splinter haemorrhages and nail-fold infarcts.

Discuss the differential diagnosis, investigation and management

The differential diagnosis includes an inflammatory autoimmune rheumatic disease such as systemic lupus erythematosus (SLE), which has developed after delivery of her baby. The lesions on her hands (Fig. 8.6) and feet are strongly suggestive of vasculitis, which is a serious prognostic factor that requires immediate therapy.

Investigations (Table 8.1) are performed to look for the possibility of major organ involvement, which might be vasculitic. Her urine must be tested immediately for blood and protein and sent for urine cytology looking for fragmented red cells and/or casts. The presence of an 'active' urine sediment with fragmented or dysmorphic red cells and granular casts has a > 90% specificity for glomerulonephritis.

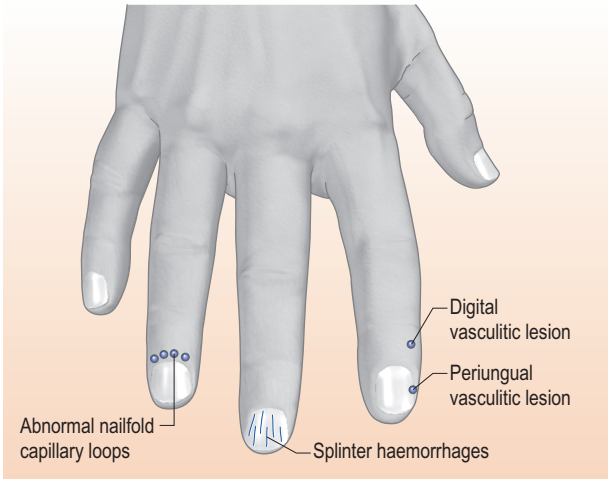


Figure 8.6 Vasculitic lesions seen in the fingers.

Table 8.1 Investigations for SLE and vasculitis

Investigation	Typical finding
FBC	Immune cytopenias, especially neutropenia and thrombocytopenia, are common in SLE
	There may be anaemia of chronic disease or haemolytic anaemia – check Coombs' test.
ESR and CRP	The pattern of a high ESR but normal CRP is characteristic of SLE
Renal function	U&E, 24-h urine protein/eGFR
Liver biochemistry	Hypoalbuminaemia is common
Lupus serology	
ANA	Present in 95% of SLE patients
dsDNA	Specific marker for SLE. A negative dsDNA, however, does not exclude SLE
ENA	Ro/La photosensitivity/Sjogren's RNP/Sm often seen in severe SLE
Complement	Low values indicate activation of complement or rarely congenital deficiency
ANCA	A marker of vasculitis: a systemic vasculitis is an alternative to SLE

Remember

The major risk of vasculitis is organ involvement including renal, cerebral and pulmonary disease, which can be life-threatening.

- **Diagnosis.** She was found to be anaemic with an Hb of 0.5 g/L, a raised ESR of 80 mm/h, normal CRP, a raised ANA and anti-ds DNA autoantibodies. A diagnosis of **systemic lupus erythematosus**.

Once the diagnosis of lupus and vasculitis is established on clinical and serological grounds, therapy is with prednisolone and IV pulse methyl prednisolone 500 mg on alternate days for three doses.

Immunosuppressive therapy is commonly used to treat vasculitis. One commonly used approach is intravenous 500 mg cyclophosphamide therapy given 2-weekly or monthly. The patient should be carefully counselled about the risks and benefits of cyclophosphamide; these include the adverse effects such as cytopenias, haemorrhagic cystitis, infections including herpes zoster and infertility. If the patient is breastfeeding she should discontinue this because cyclophosphamide and other immunosuppressives such as azathioprine are excreted in breast milk.

Remember

Specialist advice from a rheumatologist or immunologist should be sought.

- **Progress.** On treatment with steroids (see above) her symptoms settled and it was decided to delay immunosuppressive therapy until after she had stopped breastfeeding.

ACUTE AUTOIMMUNE RHEUMATIC DISEASE

Case history

A 33-year-old woman of African origin is admitted through A&E complaining of breathlessness and swollen legs. Two years ago she was admitted with a psychotic illness that had features of schizophrenia and improved with anti-psychotic medication.

In the last 6 months she has developed a symmetrical small joint inflammatory arthritis, mouth ulcers and photosensitive facial rashes. Over the last 2 weeks she has become breathless and her legs have become severely swollen.

Case history (continued)

On examination she is anaemic and has a pulse rate of 120/min with pulsus paradoxus. Her BP is 90/60. She has bilateral pleural effusions, a raised jugular venous pressure with a sharp rise and y descent (Friedreich's sign) and pitting oedema to her waist. There is synovitis of the small joints of her fingers and she has florid splinter haemorrhages. Her urine showed heavy proteinuria.

What is the likely diagnosis?

Diagnosis is likely to be **SLE complicated by the nephrotic syndrome**. In addition, she may have cardiac tamponade from a pericardial effusion.

SLE is nine times more common in females than in males, and is more common in people of African and Far Eastern ancestry; it is often more severe in these ethnic groups.

This patient has many characteristic features of SLE: inflammatory polyarthritis, mouth ulcers, photosensitive rashes, psychotic illness, serositis with pleural and probably pericardial effusions and renal disease with nephrotic syndrome (Fig. 8.7). The high JVP might indicate early tamponade.

How would you manage this patient?

The most urgent priority is whether this patient has cardiac tamponade. The low BP and the presence of pulsus paradoxus, tachycardia and raised JVP with increased distension during inspiration and cardiomegaly on CXR are strong pointers to this. An echocardiogram is performed urgently, which shows an echo free region between the myocardium and the intense echo of the parietal pericardium. This confirms the effusion and the clinical signs confirm tamponade.

The overwhelming majority of patients with lupus who have cardiac tamponade associated with a pericardial effusion respond to high-dose oral corticosteroids and do not need pericardiocentesis. This, however, should be performed if the patient deteriorates despite corticosteroid therapy or if sepsis is present. A normal CRP makes infection less likely.

The next priority is to determine the extent and severity of the renal disease. Serum creatinine, eGFR, albumin, 24-h urine protein are essential. If there is an 'active' (p. 245) urine sediment, e.g. fragmented red cells and granular casts, indicating glomerulonephritis, renal biopsy is indicated.

Investigations

- FBC with reticulocyte count/Coombs' (direct anti-globulin test) if positive: the anaemia is haemolytic
- U&Es (eGFR): renal impairment may be present
- Biochemistry: serum albumin will be low
- 24-h urine protein should be started

Continued

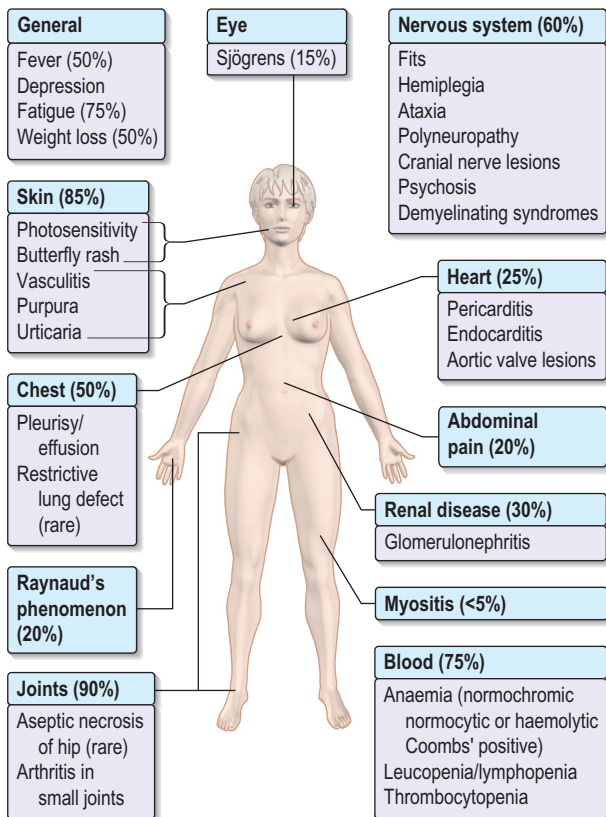


Figure 8.7 Clinical features of systemic lupus erythematosus (SLE).

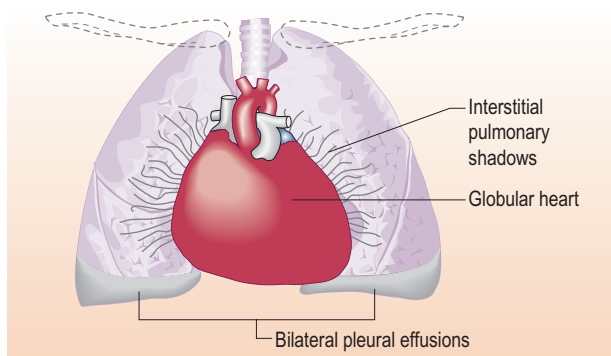


Figure 8.8 Diagram of a CXR showing pleural effusions and cardiomegaly.

Investigations (continued)

- Urine cytology for fragmented red cells and granular casts: a useful marker of glomerulonephritis
- CXR: to document pleural effusions and cardiomegaly (Fig. 8.8)
- Echocardiogram: to document pericardial effusion and possible valve lesions
- ECG
- Blood gases
- Blood cultures/urine cultures: to exclude sepsis, especially endocarditis, prior to corticosteroid and immunosuppressive therapy
- Full autoantibody screen: ANA, DNA, ENA, Rh factor, anti CCP, anti-cardiolipin antibodies, lupus anti-coagulant, ANCA
- Complement studies
- A diagnostic renal biopsy may be required later

Other points

A normal protein diet is necessary with salt restriction and diuretic therapy with a thiazide, e.g. bendroflumethiazide 5 mg daily.

- Thrombosis prophylaxis: this patient is at high risk of deep vein thrombosis (DVT)/pulmonary embolus (PE). TED stockings and prophylactic low molecular weight heparin should be given.
- Is the anaemia haemolytic? If so, it should respond to corticosteroids.
- When the blood pressure has normalised as a result of treatment of the tamponade, start an ACE inhibitor. This is especially useful in proteinuric patients.
- If renal biopsy confirms proliferative glomerulonephritis: the treatment of choice is corticosteroid therapy and intermittent intravenous cyclophosphamide followed by azathioprine.

- This patient's lipid profile might well be deranged, especially in the nephrotic syndrome. This will need to be assessed and managed actively. Measurement of serum lipids is performed and the patient started on a statin immediately if hypercholesterolaemia is present.
- Prophylaxis against corticosteroid-induced osteoporosis. A baseline dual energy X-ray absorptimetry (DXA) scan should be performed and calcium supplementation should be started.

Long-term prognosis

The majority of patients with SLE have a good prognosis, although clearly this patient has a serious disease with life-threatening complications. Mortality in SLE occurs at two peak periods: those patients who die from overwhelming disease, thrombosis or sepsis and those who die prematurely from accelerated atherosclerosis. Prognosis has been considerably improved by earlier recognition and effective therapy.

- **Progress.** This patient had several problems. Her cardiac effusion responded to high dose oral steroids gradually and her blood pressure improved. She had a haemolytic anaemia of 95 g/L. She was discharged on steroids and an ACE inhibitor after an inpatient stay of 2 weeks. She later had a renal biopsy which confirmed a proliferative glomerulonephritis and was seen by the neurologists for treatment. A DXA scan did not show osteoporosis.

Further reading

Tsokos GC. Systemic lupus erythematosus. *New Eng J Med* 2011; **365**: 2110-2121.

THROMBOSIS AND THE ANTI-PHOSPHOLIPID SYNDROME

Case history

A-25-year old woman presents with a 2-day history of left leg swelling and on the day of admission she notices breathlessness and chest pains that are worse on deep inspiration.

In her past medical history you find that she has had three miscarriages and one successful pregnancy. This pregnancy was complicated by hypertension and intrauterine growth retardation with a premature delivery at 31 weeks. On further questioning you note that she has had oral ulceration, rashes that are worse in the sunlight and has also been having headaches.

Drug history

She is on the oral contraceptive pill.

On examination

She has extensive splinter haemorrhages on most fingers. Her pulse is 100 and BP 110/70 but she is not cyanosed. Her heart sounds are normal but

there is a soft murmur of mitral regurgitation. She also has a soft left pleural rub.

Abdominal examination and neurological examination are normal. The left calf is swollen and the calf circumference is 3 cm greater than on the right. You note extensive livedo reticularis on her arms, thighs and knees.

What is the differential diagnosis and your management?

This young woman (who is on the oral contraceptive pill) has a deep venous thrombosis (DVT) and a pulmonary embolus (PE) until proved otherwise.

A full blood count revealed thrombocytopenia, which is commonly seen in the anti-phospholipid syndrome.

Investigations

- An ECG: looking for the classic (but seldom seen) S1, Q3, T3 pattern of PE (Fig. 8.9)
- A CXR: but this is likely to be normal. However, it is useful to exclude other causes of pleuritic chest pain, including infective causes
- An ultrasound scan of the leg veins to document the extent of the left calf thrombosis
- A V/Q scan to show the extent of the pulmonary emboli is still useful if CT not available
- Plasma D-dimers: if undetectable the diagnosis of PE and DVT is excluded
- Multidetector CT with contrast: good specificity 96% and sensitivity 85% for medium-sized PEs
- Choose the imaging techniques according to local availability

An echocardiogram and blood cultures in women are essential because differential diagnosis includes Libman-Sacks endocarditis or infective endocarditis.

Differential diagnosis

In this case this includes the anti-phospholipid syndrome with a DVT and pulmonary emboli, along with an increased risk of thrombosis from the oral contraceptive pill. The history is rather suggestive of SLE, and this should be investigated further with autoantibodies to ANA, DNA and ENA with complement studies. The features favouring a diagnosis of the anti-phospholipid syndrome in this case would include the three previous miscarriages and one pregnancy complicated by intrauterine growth retardation and premature delivery. There is accumulating evidence in the literature to suggest that the intrauterine growth retardation is due to recurrent placental thrombosis and this is often manifested by reduced umbilical artery flow patterns on Doppler studies, with an increased resistance index, notching or even reversed flow in the umbilical vessels.

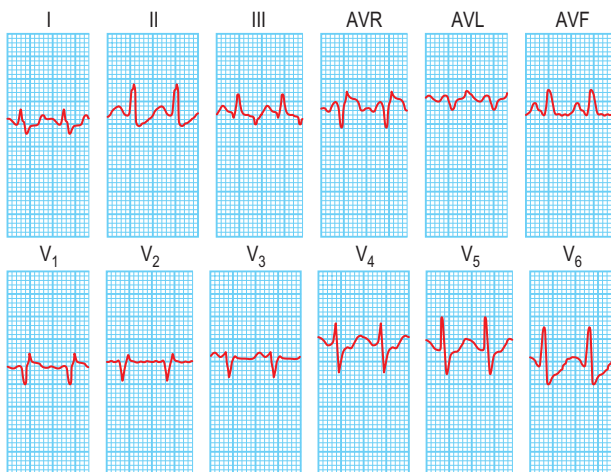


Figure 8.9 Acute pulmonary embolism shown by a 12-lead ECG. There is an S wave in lead I, a Q wave in lead III and an inverted T wave in lead III (the S1, Q3, T3 pattern). There is sinus tachycardia (160 bpm) and an incomplete right bundle branch block pattern (an R wave in AVR and V₁ and an S wave in V₆).

Information

- The anti-phospholipid syndrome is due to the presence of antibodies that bind phospholipids, leading to both venous and arterial occlusion
- The syndrome is most commonly seen in SLE but can occur in isolation: primary anti-phospholipid syndrome

The anti-phospholipid syndrome

Anti-cardiolipin antibodies and the lupus anti-coagulant should be performed. Both the anti-cardiolipin antibodies and the lupus anti-coagulant are anti-phospholipid antibodies and both should be requested because a small percentage of patients have either one or the other antibody but not both. A thrombophilia screen can exclude other factors, including the factor V Leiden mutation. Patients with the anti-phospholipid syndrome also have reduced protein C and S levels, which are associated with the lupus anticoagulant.

Libman-Sacks endocarditis

Splinter haemorrhages and a mitral murmur indicate Libman-Sacks endocarditis, which is a feature of the anti-phospholipid syndrome and SLE.

These patients get a mucinous degeneration of the mitral valve leaflets and occasionally thrombus (which might embolise) is seen on the damaged valves. Similarly, the damaged valves might become secondarily infected, leading to infective endocarditis. The splinter haemorrhages could represent micro-emboli and are a feature of both anti-phospholipid syndrome and infective endocarditis.

How would you manage this patient?

- **Progress.** This woman should be admitted and commenced on heparin. The heparin can be given intravenously as a continuous infusion but many hospitals use once-daily low molecular weight heparin. Warfarin should be commenced and the eventual target INR should be 2.5.

The diagnosis of the anti-phospholipid syndrome was confirmed and therapy with life-long warfarin at the target INR was started. These patients are often resistant to warfarin and occasionally require high doses, e.g. 15–20 mg warfarin daily.

In terms of the mitral valve disease, this patient needed counselling about appropriate antibiotic therapy for any infection. Prophylactic antibiotics are not required. Infective endocarditis was excluded and she was monitored regularly because a small percentage of these patients require mitral valve replacement.

Further reading

Hughes GRV. Hughes' syndrome: the anti-phospholipid syndrome. *Journal of the Royal College of Physicians of London* 1998; **32**: 260–264.

Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. *Lancet* 2010; **376**: 1498–1509.

CRYSTAL ARTHRITIS

Two main types of crystal account for the majority of crystal-induced arthritis. They are sodium urate (gout) and calcium pyrophosphate (pseudogout) and are distinguished by their different shapes and refringence properties under polarized light with a red filter. Rarely, crystals of calcium apatite or cholesterol cause acute synovitis.

Case history

A 73-year-old woman was admitted a week ago to the Stroke Unit, having had a right hemiparesis. She has developed a hot, swollen right knee. You have been asked to see the patient for your advice on whether this might be a septic arthritis.

On further questioning, you discover that the patient has attended the hypertension clinic for many years and has been taking bendroflumethiazide. She has also complained of knee pain intermittently over the last 5 years but the joint has never previously swelled up. She is making a reasonable recovery from her stroke and there is no other relevant history.

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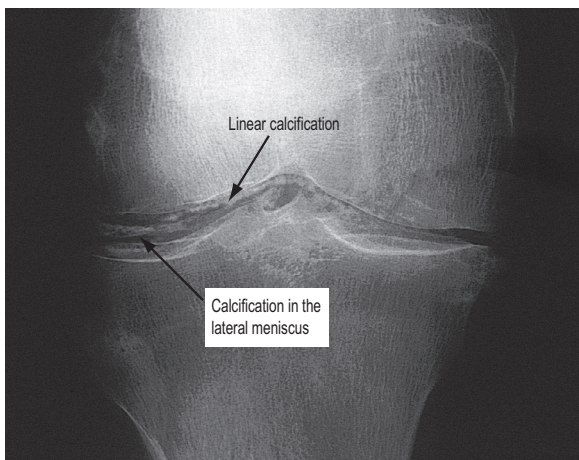


Figure 8.10 Chondrocalcinosis of the knee. Note the linear calcification in the hyaline cartilage and calcification of the lateral meniscus (plus mild secondary OA).

Case history (continued)

Clinically, there is no evidence of tophi. The knee is hot and movement is restricted due to a large tense effusion. She is afebrile.

How would you manage this patient?

The X-ray showed chondrocalcinosis (Fig. 8.10) and patello-femoral and tibio-femoral osteoarthritis. The serum uric acid was elevated ($520 \mu\text{mol/L}$); she is taking a thiazide diuretic. The differential diagnosis thus includes gout or pseudo-gout, of which pseudo-gout is probably more likely in this clinical context. The uric acid level, although high, is usually $> 600 \mu\text{mol/L}$ with gout.

Investigations

- Full blood count
- ESR
- U&Es
- Bone and liver biochemistry
- Serum urate
- X-ray of the knee
- Blood cultures
- The joint should be aspirated with a sterile technique and fluid sent for cells, crystals and culture

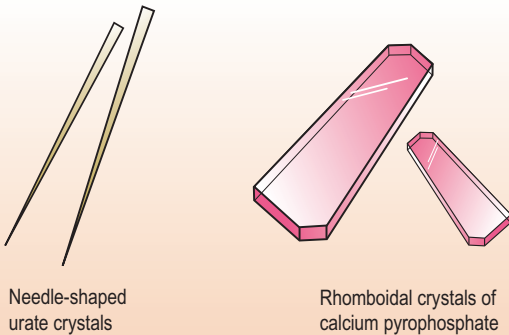


Figure 8.11 Calcium pyrophosphate and urate crystals.

Pseudo-gout

This patient has the typical presentation of pseudo-gout – an acute onset of a swollen joint in an elderly patient who has been admitted for other reasons – usually a stroke, MI or chest infection.

Calcium pyrophosphate is the most common crystal associated with pseudo-gout (Fig. 8.11). The crystals are diagnosed on synovial fluid analysis using polarised light microscopy. They are rhomboidal and positively birefringent and can be idiopathic or associated with osteoarthritis. A number of metabolic conditions are also associated with calcium pyrophosphate deposition; these include hypothyroidism, hyperparathyroidism, acromegaly, Wilson's disease, haemochromatosis, hypophosphatasia and hypomagnesaemia.

The differential diagnosis of gout is also confirmed on crystal examination. These urate crystals are negatively birefringent needle-shaped crystals.

Management

Septic arthritis, although unlikely, should be excluded and, providing joint aspiration and synovial fluid culture and blood cultures are all negative, the knee should be aspirated to dryness and injected with a steroid such as 40 mg of methylprednisolone. Risk factors should be minimised and, in particular, the thiazide diuretic (which can precipitate gout) should be switched to an alternative anti-hypertensive medication. Intensive physiotherapy is necessary, with particular attention to quadriceps exercises and maintaining mobility and hydration in the patient.

- **Progress.** She was started on diclofenac 50 g × 3 daily and was able to be gradually mobilised with the help of physiotherapy. Her speech improved over the first 2 weeks but she was left severely disabled by her right sided weakness. She was eventually transferred to long-term care.

Further reading

Neogi T. Gout. *N Engl J Med* 2011; **364**: 443–452.

POLYMYALGIA RHEUMATICA/CRANIAL ARTERITIS

Polymyalgia rheumatica (PMR) and giant cell (cranial) arteritis are a systemic vasculitis affecting people over 50 years of age. Both are associated with the finding of a giant cell arteritis on temporal artery biopsy.

Case history

A 73-year-old woman presents to A&E feeling non-specifically unwell. On further questioning she has a headache and joint aches, particularly of her shoulders and hips, in addition to widespread aches and pains. She has marked joint stiffness particularly of the shoulders and hips, lasting for several hours each morning, and occasionally all day. The headache is predominantly right-sided and the patient says that it is painful when she brushes her hair. In addition, she has pains in the left jaw on talking or eating.

On examination the scalp is tender and it is difficult to palpate the temporal arteries. The rest of the examination is normal. Her shoulders and hips ache at the extremes of the range of movement but are otherwise normal.

Differential diagnosis and management

The most likely diagnosis in a patient over 50 years is temporal arteritis with PMR and there is therefore a significant risk of blindness from arteritis of the ophthalmic artery. A differential diagnosis includes malignancy of any cause and myeloma which can, rarely, mimic PMR. The ESR is nearly always significantly elevated but approximately 1–5% of patients with polymyalgia rheumatica have a normal ESR.

Investigations

The following investigations are essential:

- Full blood count
- ESR or CRP
- U&Es
- Liver biochemistry
- Temporal artery biopsy

This patient should be commenced on 60 mg of prednisolone immediately and a temporal artery biopsy should be arranged within the next 24 h. The clinical diagnosis is **giant cell arteritis**.

The histological features of GCA are:

Histological features of cranial arteritis

- Intimal hypertrophy
- Inflammation of the intima and sub-intima
- Breaking up of the internal elastic lamina
- Giant cells, lymphocytes and plasma cells in the internal elastic lamina

The response to steroids is usually dramatic in these patients and a response is often seen within 24–48 h. The steroid therapy can then be reduced reasonably quickly, over a few months, to 15–20 mg daily, and if this is not possible, then a steroid sparing agent such as azathioprine should be added to achieve this. The addition of low-dose aspirin may reduce the risk of blindness. This patient is also at high risk of osteoporosis and subsequent vertebral fractures, and calcium and vitamin D supplementation should be co-prescribed routinely. A baseline DXA should be requested. If there is already osteoporosis, bisphosphonates should be given.

- **Progress.** This patient's headache quickly went on steroid therapy and in 6 months she was well on prednisolone 10 mg daily with a normal ESR. Her steroids will be continued for at least 1 year, with regular checks of her ESR.

Patients who fail to respond to steroids

Such patients should be investigated in detail for an underlying malignancy, especially multiple myeloma. Occasionally, other conditions such as severe hypothyroidism might also present with similar joint aches but the clinical picture of temporal arteritis with a good response to steroids is usually characteristic enough to establish the diagnosis.

ACUTE BACK PAIN

This is usually due to acute lumbar disc prolapse. The central disc gel may extrude into a fissure in the surrounding fibrous zone and cause acute pain and muscle spasm, which in turn leads to a forwards and sideways tilt when standing.

Case history

A 36-year-old publican presents to A&E having just lifted a barrel of beer. He experienced severe buttock and back pain. The pain radiated down the left leg to the sole of the foot with associated paraesthesiae. On further questioning he finds that it is extremely painful to move his back and that the pain is worse on coughing or sneezing. The pain is also worse in the leg than in the back. He says that he has not passed any urine for 6 h.

On examination

He is in severe pain and is lying flat on the examination couch. He finds it too painful to stand up but the hips, knees and other joints are all normal on examination. Straight leg raising on the right is 40° and on the left is only 10°, with a strongly positive sciatic stretch test. The femoral nerve stretch test is also strongly positive on the left and neurological examination reveals an absent left ankle jerk and sacral anaesthesia.

Discuss your further investigations, diagnosis and management

The history and clinical examination are almost diagnostic for a large L5/S1 disc protrusion with compromise of the cauda equina, which can lead to urinary retention. This is therefore a neurosurgical emergency.

The most urgent investigation is imaging of the lumbar spine and pelvis; magnetic resonance imaging (MRI; Fig. 8.12). The patient should be catheterised and analgesia given. This includes intramuscular non-steroidals such as IM diclofenac or opiate analgesics including morphine if needed. The patient should be referred immediately to a neurosurgeon or orthopaedic surgeon with an interest in acute spinal problems for urgent decompressive surgery with a laminectomy and discectomy. Any delay in diagnosis or decompression might lead to a permanent neurological deficit.

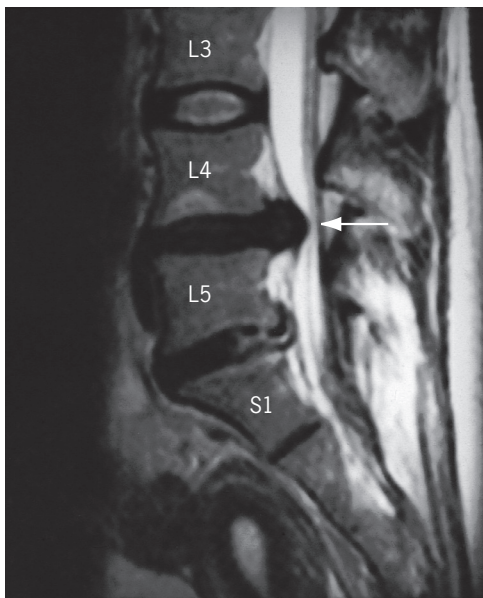


Figure 8.12 MRI of lumbar spine showing a central disc prolapse at the L4/L5 level (arrow). The signal from the L4/L5 and L5/S1 discs indicates dehydration, whereas the appearance of the L3/L4 signal is normal.

In patients without sacral anaesthesia or neurological deficit, the evidence-based advice is not to recommend bed rest but to mobilise the patient as soon as possible using adequate analgesia. Rapid access to physiotherapy can improve outcome, and procedures such as sacral or lumbar epidurals might be necessary to relieve pain while recovery occurs.

- **Progress.** This patient required urgent surgery as the MRI showed a large L5/S1 disc protrusion. He made a good recovery and had no permanent neurological deficit.

SEVERE BACK PAIN/OSTEOPOROSIS

Osteoporosis is characterised by reduced bone density and micro-architectural deterioration of bone tissue, leading to increased bone fragility and the susceptibility to fracture.

Case history

A 71-year-old woman presents with severe thoracic spinal pain, which came on suddenly 6 h previously. The pain is severe and radiates around the thoracic spine and front of the chest and is worse on coughing or sneezing. In the past medical history she has had rheumatoid arthritis for the last 25 years and is currently taking 7.5 mg of prednisolone daily. Her rheumatoid arthritis has been in remission for 5 years on this therapy and she is on no other medication. Disease-modifying drugs used in the past have either induced toxicity or have been ineffective.

On examination there is evidence of quiescent rheumatoid arthritis with classic rheumatoid deformities, nodules and synovial thickening, but no active synovitis. On examination of the thoracic spine there is a marked kyphosis and she is exquisitely tender over T8. The thoracic spine is markedly restricted on rotation, reproducing her pain radiating around the chest to the anterior aspect of the chest.

What investigations would you do?

Investigations

- Full blood count
- ESR
- Renal function
- Bone and liver biochemistry
- C-reactive protein
- X-ray chest and thoracic spine

Discuss your differential diagnosis and management in this case

The most likely diagnosis is steroid-associated osteoporosis with an acute vertebral fracture. The differential diagnosis should include myeloma

and other malignancies because these can also present with vertebral fractures.

Imaging should include a chest X-ray and specific views of the dorsal spine, which are likely to show one or more vertebral crush fractures. Crush fractures have a fairly characteristic appearance and on the AP view of the thoracic spine all the pedicles should be visible. Should any pedicles be missing, this should immediately raise the suspicion of metastatic malignancy as a cause of the vertebral fracture.

Later, a myeloma screen including a protein electrophoresis strip, serum light chain assay and urine for Bence Jones protein should be done.

A DXA scan is performed to establish the degree of osteoporosis (Fig. 8.13). This gives an accurate index of bone mineral density in relation to the normal range for an age-, sex- and race-matched population. The World Health Organization definition of osteopenia is a T score of between -1.5 and 2.5 . The definition of osteoporosis is a T score of greater than -2.5 standard deviations below the mean and established or severe osteoporosis is a T score of greater than -2.5 with an established fracture.

Initial management

In the acute setting of a recent vertebral fracture, strong analgesia, e.g. meptazinol 200 mg every 3–6 hours intramuscularly or intravenously if

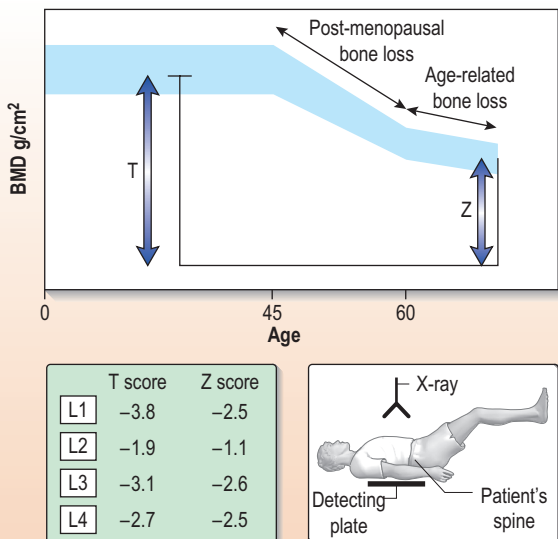


Figure 8.13 DXA scan. Graph showing BMD (vertical axis) against age. T score = number of standard deviations that patient's BMD differs from population average for healthy young adult. Z score: as T score but BMD deviations from population average for patient's age.

necessary. Salmon calcitonin 50 units daily, increasing to 100 units intramuscularly or 200 units daily by nasal spray for 6 weeks has a very good analgesic effect and works rapidly. Its main adverse effects include hypotension and flushing with nausea although most patients are able to tolerate 50 units daily. A single intravenous infusion of a bisphosphonate (pamidronate 60–90 mg) also gives some pain relief.

- **Progress.** This woman's pain proved difficult to control and kyphoplasty was performed. This involves injecting methyl methacrylate through a needle placed directly into the damaged vertebra. This allowed mobilisation with physiotherapy help.

Later management

This patient should commence specific therapy for osteoporosis.

Therapies include cyclical etidronate with calcium or weekly alendronate or risedronate. These therapies are well tolerated in this age group but alendronate and risedronate are associated with a small but significant risk of oesophagitis. All the bisphosphonate drugs are poorly absorbed and should be taken at least 2 h before a meal with a full glass of water and, in particular with alendronate, the patient should not lie down for at least 2 h after taking the medication to reduce the risk of oesophagitis. Strontium ranelate is used in post-menopausal osteoporosis. These medications increase bone mineral density over a 3- to 5-year period and also reduce fracture risk.

Hormone replacement therapy (HRT) is not usually used in women of this age because of the adverse effects, which include breast tenderness and a return of menses. Raloxifene, a selective oestrogen-receptor modulator (SERM) has been shown to increase bone mineral density. The main adverse effects of raloxifene include a risk of thrombosis and possible endometrial/uterine malignancy. There is evidence that raloxifene protects against the risk of breast cancer.

Other factors used in the treatment of osteoporosis include stopping smoking, keeping alcohol intake to a moderate level and encouraging active weight-bearing exercise. Attention to diet is necessary, particularly in this age group, and a broad varied diet containing a reasonable calcium intake should be advised; if necessary a specific dietitian referral would be helpful. These patients should be monitored with DXA scan to check on progress.

- **Progress.** This woman had not been given prophylactic bisphosphonate therapy, which is usually necessary in addition to calcium for patients on long-term steroids. Nor did she have regular DXA scans to assess the development of osteoporosis.

Her prednisolone 7.5 mg daily was gradually tapered and stopped and her RA remained in remission, with some analgesia with an NSAID being required. She has continued on alendronate calcium and has regular DXA scans.

OSTEOMYELITIS

Case history

A 56-year-old Asian woman presents with a 2-month history of upper back pain and weight loss. She has just arrived home after visiting relatives in Bangladesh for the last year.

There is no relevant past history and she is taking no medication.

On examination she is in pain and looks thin. Her pulse is 110 per minute and regular; her temperature is 38°C. Cardiovascular, respiratory and abdominal examinations are all normal and neurological examinations including power, tone and reflexes are within normal limits. There are no sensory signs.

All her joints are normal but she is tender over the thoracic spine, which is exquisitely painful on rotation of the thoracic spine.

Investigations

- Hb 106 g/L, MCV 83
- ESR 102 mm/hour, CRP 94
- U&Es normal
- Biochemistry – Serum Ca 2.3 mmol/L; phosphate 1.2 mmol/L; serum alkaline phosphatase 103 IU/L

A thoracic spine radiograph was normal. A chest X-ray showed no evidence of tuberculosis.

What is the differential diagnosis?

The differential diagnosis is **spinal tuberculous osteomyelitis** (Pott's disease) despite the normal chest X-ray. A differential diagnosis would include *Staphylococcus aureus* discitis, although this tends to affect the lumbar spine whereas tuberculous spinal disease characteristically affects the thoracic spine or the thoraco-lumbar junction.

The most useful investigation is an MRI scan of the thoracic spine. This showed destruction of the vertebral body T4 with evidence of discitis T4/T5. A paravertebral abscess accompanied the bone destruction. These findings are typical of thoracic spine tuberculosis. There was no evidence of cord compression so a neurosurgical opinion was not required. Aspiration of the vertebral abscess was carried out to culture the tubercle bacillus and to obtain the sensitivities. She was commenced on isoniazid, pyrazinamide, rifampicin and ethambutol, to be given for 9 months (reducing drugs when sensitivities known, p. 362). Other risk factors should always be considered, such as immunosuppression and HIV disease.

As vertebral collapse was not present, the prognosis is usually excellent in these patients if the organism is fully sensitive to therapy and compliance with therapy is maintained.

- **Progress.** This patient made an excellent recovery and was left with no sequelae from her spinal abscess.

SEPTIC ARTHRITIS

Septic arthritis is due to haematogenous spread from skin or a respiratory tract infection. It is also seen occurring after surgery or sometimes following trauma to the joint.

Case history

A 21-year-old man presents with pain and swelling of his right knee. On further questioning he had no other symptoms. He had no relevant past medical history. Specifically, he has had no diarrhoea, urethritis, rashes or oral ulceration and has had no problems with inflammation of his eyes. His sexual history revealed many sexual contacts, including oral/anal sex with other men.

How would you investigate and manage this patient?

The most common diagnosis in a young man with a monoarthritis is a reactive arthritis associated either with diarrhoea or with urethritis, usually chlamydial in origin (Fig. 8.14). However, clinical questioning with this man has excluded any associated features that would point to reactive arthritis (a triad of urethritis, arthritis and conjunctivitis – Reiter's disease) and septic arthritis should be considered as the most likely diagnosis, raising the possibility of HIV disease.

Investigations

- Full blood count normal
- ESR 74 mm/1 hour
- Biochemistry, including a serum uric acid 420 $\mu\text{mol/L}$

The joint should be X-rayed and a series of blood cultures performed following admission to MAU.

Using sterile technique the joint should be aspirated and the fluid sent for microscopy, culture and crystals.

Information – knee aspiration

- Explain procedure and obtain consent
- Strict aseptic technique
- 2% lidocaine as local anaesthetic
- Medial or lateral approach 0.5–1 cm below the patella
- Use a white needle to ensure that even viscous or purulent fluid can be aspirated easily
- Caution in patients on warfarin
- Do not inject steroids if fluid is purulent

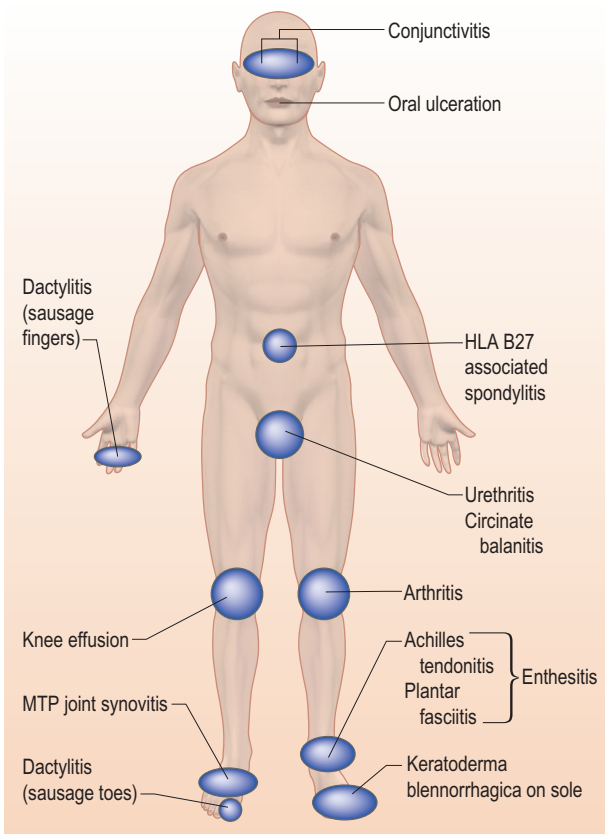


Figure 8.14 Clinical features of reactive arthritis.

The most common organism is *Staphylococcus aureus*, which is seen in between 40% and 70% of patients. Gram-negative organisms are the next most common but a careful search for gonorrhoea should be conducted and the patient should be referred to the genitourinary medicine clinic for urethral swabs and other tests.

This man is at risk for HIV and should be counselled carefully before arranging an HIV test. Should HIV be proven then microbiology assessment of the synovial fluid is crucial, particularly for atypical organisms such as *Mycobacterium avium intracellulare* and other forms of tuberculosis.

Table 8.2 Examination of synovial fluid

Characteristics of synovial fluid	Diagnosis	WCC per mm ³
Colour: clear, yellow and viscous	Osteoarthritis	< 3000
Translucent and thin Very cloudy	Rheumatoid arthritis Seronegative arthritis Reactive arthritis (Reiter's disease) Crystal arthritis	3000–40 000
	Sepsis	750 000
Polarised light microscopy with a red filter needs to be undertaken by an expert: <ul style="list-style-type: none"> • gout: negatively birefringent, needle-shaped crystals of sodium urate • pyrophosphate arthropathy (pseudo-gout): rhomboidal, weakly positively birefringent crystals of calcium pyrophosphate 		
Gram staining is essential if septic arthritis is suspected and may identify the organism immediately. Joint fluid should be cultured and antibiotic sensitivities requested		
The fluid can be examined directly in a clear syringe or sterile pot. The characteristics of synovial fluid show a trend from clear to purulent, which indicates roughly the type of arthritis.		

From Kumar and Clark *Clinical Medicine* 7th edn, 2009.

- **Progress.** In this man, a septic arthritis was confirmed on blood and synovial fluid culture (Table 8.2) due to *Staph. aureus* infection. He required 6 weeks of intravenous antibiotics, flucloxacillin plus oral fucidic acid. Arthroscopic drainage and washout of the joint was performed at 48 hours, which minimised joint damage.

He made a good recovery.

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PRESENTATION OF KIDNEY AND URINARY TRACT DISEASE

- Patients' complaints are directly related to the urinary tract or urine output, e.g. frequency, dysuria, burning micturition, urgency, colic, polyuria, nocturia, haematuria, oliguria, and anuria.
- Discovery of abnormal laboratory findings during routine investigations, e.g. proteinuria, haematuria, elevated plasma creatinine, electrolyte and acid-base disturbances.
- Symptoms and signs of renal failure (e.g. uraemia, anaemia, anuria, hypertension and oedema) in the absence of prior renal disease.
- Discovery of renal and urinary tract disease as part of involvement in systemic disease, for example:
 - Metabolic disease (e.g. diabetes mellitus): the most common cause of end-stage renal disease (ESRD) in the Western world
 - Autoimmune rheumatic diseases (e.g. SLE, vasculitis, systemic sclerosis, rheumatoid arthritis)
 - Infectious diseases (e.g. Gram-negative sepsis, infective endocarditis, mycobacterial, protozoal, viral)
 - Cardiovascular diseases (e.g. hypertension, heart failure)
 - Blood dyscrasia (e.g. multiple myeloma, amyloidosis, lymphoma, HUS/TTP).

Information

- Decline in GFR: is this due to pre-renal, post-renal or intra-renal disease?
- Intrinsic renal disease: divide into glomerular or non-glomerular disorders (e.g. tubular, interstitial or vascular)
- Differentiate between primary renal diseases and renal disorders secondary to systemic disease
- Identify preventable or reversible diseases

FLUID BALANCE AND ELECTROLYTES: ASSESSING FLUID STATUS

Clinical assessment

Take a quick history, particularly of fluid and electrolyte intake (oral or intravenous) and output (renal, GI tract or skin), then examine the patient (Fig. 9.1, Table 9.1).

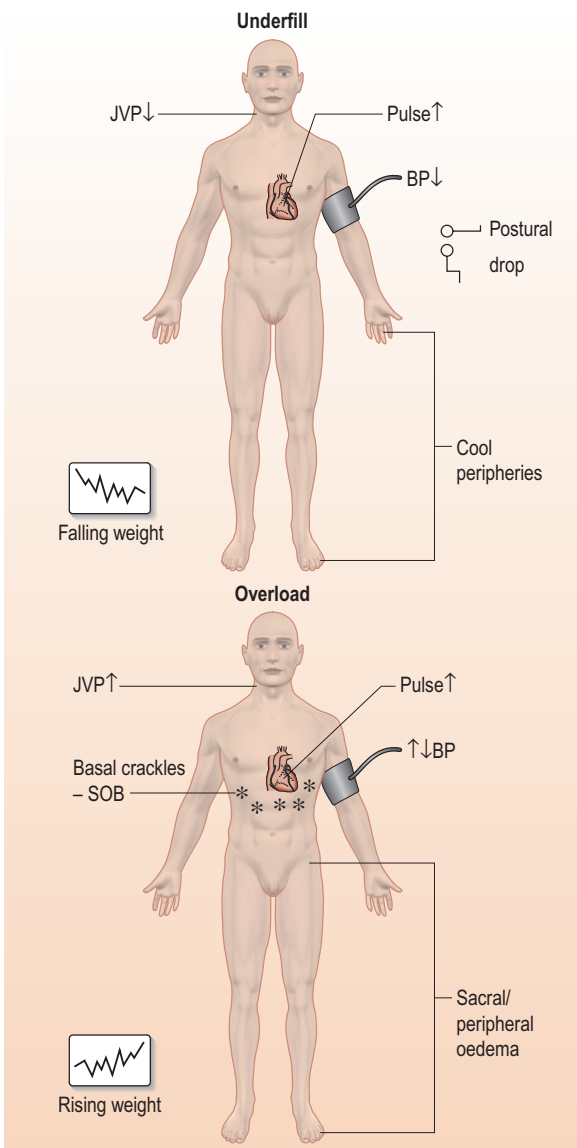


Figure 9.1 Examining the patient: underfill and overload.

Table 9.1 Tools to assess fluid status

	Useful	Not so useful
Clinical examinations	BP (especially postural or post-exercise drop) Oedema JVP Peripheral perfusion Pulse Basal crackles	Skin turgor Eye turgor Mucous membranes
Charts	Serial weight (on same machine)	Fluid balance (input/output)
Additional tools	CVP line – use dynamically CXR Pulmonary artery flow catheter	CVP – absolute Urine Na ⁺ Osmolality

Case history (1)

A 43-year-old man is brought to A&E with a 4-day history of severe abdominal pain and watery diarrhoea up to 10 times daily. He has felt so bad that he has hardly drunk or eaten anything over the last few days. He has lost 5 kg in weight.

He is normally fit and well and he wonders whether he has some form of severe gastroenteritis.

On examination he is dehydrated with dry tongue. Abdominal examination reveals some generalised tenderness.

Figure 9.1 (a) shows the other signs of hypovolaemia.

Investigations

Serum Na 123 mmol/L

Serum K 2.1 mmol/L

Chloride 86 mmol/L

Urea 35 mmol/L

Creatinine 120 µmol/L

Hb 154 g/L

PCV 0.58.

- **Diagnosis.** Dehydration, secondary to gastrointestinal fluid loss plus pre-renal failure.
- **Management:** Volume replacement can often be achieved with oral rehydration solutions but because of hypotension, this man was given intravenous 0.9% saline initially over 1 hour, followed by 1 litre of 0.9% saline plus 20 mmol K⁺ 4-hourly for 24 hours. He quickly improved and clinically appeared euvolaemic (normal venous pressure, pulse and blood pressure) by the next day. (NB. Stool cultures grew *Campylobacter*, which is a common cause of severe gastroenteritis.)

Remember

- Examine the patient again!
 - Then again later (today)!!
 - And again (tomorrow)!!!
- Laboratory tests are no substitute for clinical assessment.

Case history (2)

A 24-year-old man is involved in an RTA, receiving injuries to his chest and abdomen.

On admission to the Trauma Unit he is shocked, with a tachycardia of 120 bpm, BP 90/55 and cold, clammy peripheries. His GCS score is 12.

Examination of his chest reveals a right haemothorax. Abdominal examination shows a tender, rigid abdomen with no bowel sounds, suggestive of peritonitis.

Management

Airways, circulation and breathing were quickly assessed and ventilation started with a very tight-fitting facial mask.

Intravenous access was achieved with a large bore intravenous cannula and 0.9% saline started. A urinary catheter was inserted.

An emergency CT scan confirmed the haemothorax and an intercostal tube drain was inserted.

Abdominal CT confirmed free fluid in the abdomen and an abnormal small intestine, suggestive of ischaemia. Liver, spleen and other organs seemed normal.

A CVP line was inserted to assess fluid balance. Fluid challenge (Table 9.2 and Fig. 9.2) indicated hypovolaemia, and blood transfusion (2 units) was started with repeated checks on his fluid status.

A laparotomy was performed and 20 cm of small bowel resected.

On post-op, his vital signs were stable but he had not passed urine despite intravenous furosemide and adequate fluid replacement. His urea and creatinine have risen, indicating acute kidney injury due to acute tubular necrosis.

Table 9.2 Fluid challenge

Use CVP dynamically (Fig. 9.2). Take reading



Give IV bolus (100 mL 0.9% saline) fluid challenge



Repeat reading

CVP ↑ – full

CVP ↓ – not full

There is no absolute value

Do this yourself! If done correctly this gives accurate information

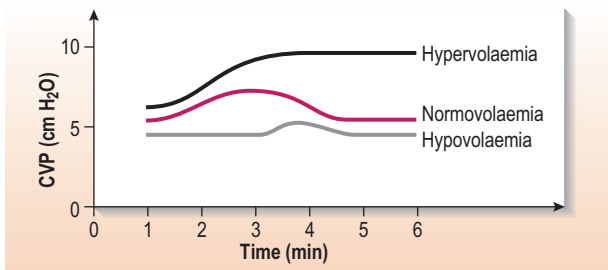


Figure 9.2 Fluid challenge.

Further management is provided by the Renal Unit with the aim of controlling fluid and electrolyte balance, and treatment of sepsis until the kidneys spontaneously recover. After 10 days' management, including haemofiltration (necessary for uncontrolled hyperkalaemia), he started to pass urine and eventually made a good recovery.

FLUID BALANCE AND ELECTROLYTES: SODIUM PROBLEMS

What are you actually measuring when you measure the serum sodium?

A ratio of:

- Extracellular Na⁺ in mmol
- Extracellular water in litres.

Using this concept you can describe how serum Na⁺ becomes abnormally low (hyponatraemia) or high (hypernatraemia) (Table 9.3).

How do I work out why?

The key is to determine the extracellular water. Examine the patient (see Fig. 9.1).

Hyponatraemia

This is defined as sodium < 135 mmol/L.

Table 9.3 Hyponatraemia and hypernatraemia

Ratio (Na ⁺ : water)	Extracellular water
Hyponatraemia Water ↑ Water ↑ > Na ⁺ ↑ Na ⁺ ↓	→ or ↓ ↓↓ ↓
Hypernatraemia Water ↓ Water ↓ > Na ⁺ ↓ Na ⁺ ↑	→ or ↓ ↓↓ ↑

Case history

The gynaecology SHO is worried about a 53-year-old woman who is 3 days post-op after a transabdominal hysterectomy. Her serum Na^+ has fallen to 123 mmol/L. The SHO asks whether the woman should be given some 1.8% (twice-normal) saline? The polite answer is No!

Remember

Wherever sodium goes, water is sure to follow, and vice versa.

Management

- Fluid assessment
- Examine fluid charts.

On examination there were no features of fluid depletion, which excludes true Na^+ depletion.

You then discover that she had been receiving 5% glucose by IV infusion since surgery 3 days ago. This is probably the most common cause of hyponatraemia in a surgical patient.

Action

- Stop IV fluids, restrict oral fluids to 1 litre daily and food as requested by the patient. 48 hours later her serum sodium is 132 mmol/L.

Other causes of hyponatraemia

- Diuretic therapy: particularly loop diuretics cause large renal losses of salt and water and metabolic alkalosis.
- Severe heart failure, advanced liver cirrhosis or nephrotic syndrome: hyponatraemia with increased total body sodium and even greater excess of water resulting in ascites and oedema. Plasma osmolality is low. Increased water orally continues in the face of salt restriction, diuretic therapy or both and will aggravate the ascites and oedema.
- Syndrome of inappropriate ADH production (p. 459).
- Pseudohyponatraemia: e.g. hyperlipidaemic states where sodium is confined to the aqueous phase or monoclonal gammopathies, hyperglycaemia (10 mmol rise reduces sodium by approximately 2 mmol).

Further reading

Sterns RH, Hix JK, Silver S. Treatment of hyponatraemia. *Curr Opin Nephrol Hypertens* 2010; **19**(5): 493–498.

Hypernatraemia

Case history

A 47-year-old man is in the Neurosurgical Unit, having had a pituitary tumour removed by trans-sphenoidal surgery. He has made a normal postoperative recovery but on review prior to discharge he complains of excess thirst and nocturia.

Review of the fluid balance charts show that he is drinking nearly 5 litres a day, with a urinary output of 3.5 L.

Recent blood tests show a serum Na^+ of 153 mmol/L.

You diagnose cranial diabetes insipidus which you know occurs transiently for a few days or weeks after pituitary surgery.

Hypernatraemia is defined as sodium > 145 mmol/L.

- Iatrogenic: IV infusion of hypertonic sodium bicarbonate, hyperalimentation by IV route or nasogastric tube, sodium chloride tablets, sea water drowning or mineralocorticoid excess; total body sodium is elevated in these conditions. Signs are of hypervolaemia.
- Impaired thirst/unconscious patient: total body sodium is low because of both sodium and water deficit but water losses are greater than the losses of sodium. Signs are of hypovolaemia.
- Osmotic diuresis, e.g. diabetic ketoacidosis, radiocontrast, mannitol: total body sodium is low because of both sodium and water deficit, but water losses are greater than sodium losses. Urine is not maximally concentrated despite hyperosmolar state, in contrast to GI losses of sodium and water where urine is maximally concentrated. Signs here are of hypovolaemia.
- Water loss, e.g. diabetes insipidus: normal total body sodium. Signs are of euvolaemia.

Remember

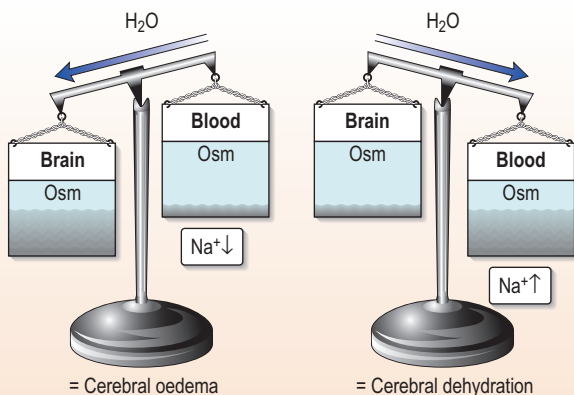
True Na^+ overload is invariably iatrogenic and gives a clinical picture of fluid overload.

Treatment

- Reassure the patient
- Avoid rapid correction (Fig. 9.3). Serum Na^+ should not fall > 1 mmol every 2 hours, i.e. 10 mmol/24 hours.
- Initially give IV 0.45% saline. This is followed by 5% glucose with 20 mmol/L K^+ with frequent monitoring of volume status and serum Na^+ level. This stays in the extracellular compartment (see assessing fluid status, p. 223).

Key points

- Examine the patient: know where their water is.
- Slow correction.


Rapid correction = risk of brain damage

↑ Osmolality by > 2 mOsm/h

– risk of osmotic demyelination syndrome (ODS)

↓ Osmolality by > 2 mOsm/h

– risk of cerebral oedema

(normal plasma osmolality = 270–290 mOsm/kg)

Figure 9.3 Effect on the brain of changes in sodium concentration.

- Hyponatraemia is a more common problem in clinical practice than hypernatraemia.
- Hypernatraemia is generally found in ITU patients.

PATIENT STOPPED PASSING URINE

Information

- Oliguria: urine output < 500 mL/day
- Anuria: urine output < 50 mL/day

Case history

The surgical house officer calls you at 10 p.m. to say that she has a 62-year-old man who is 2 days post-laparotomy and who isn't passing urine.

What should you do?

- Do: see the patient.
- Don't: simply give telephone advice.

Take a detailed history of type of surgical procedure. Ask about GI bleeding, dehydration or other fluid losses, nephrotoxic drugs, drugs associated with hypersensitivity reaction causing tubo-interstitial nephritis (e.g. penicillins, NSAIDs, cephalosporins), evidence of previous renal insufficiency, and any radiological procedure with contrast enhancement. Anuria usually means obstructive uropathy or vasculitides rather than acute tubulo-nephritis (ATN); evidence of these conditions should be sought.

On examination the patient has a tachycardia of 110 bpm with a low BP 90/50.

Examination of his abdomen shows a healing laparotomy scar, no tenderness and no evidence of a palpable bladder.

Common causes of poor urinary output

- Urine retention: always catheterise.
- Dehydration: assess fluid status (see Fig. 9.1). Look at fluid balance charts.
- Shock: see Table 9.4.
- Drugs: look at medicines chart.

Results in this man

- No urine from catheter
- Your clinical assessment – hypovolaemic
- Fluid charts incorrectly filled in but patient seems to have received 2 litres of fluid (intravenous and oral) over the last 48 hours.

Initial management

This man is fluid depleted and needs fluid replacement (Table 9.5):

- 0.9% saline IV (20 mmol/K⁺) added to each litre
- Write up initial regimen: modulate according to patient age, size and severity
- Reassess fluid status regularly
- When in doubt use a CVP line.

Aim

To establish a diuresis of at least 100 mL per hour. In most cases, a failure to achieve this is because of inadequate fluid replacement.

Table 9.4 Shock – failure of organ perfusion

	BP	Peripheral perfusion	CVP	Brief action
Hypovolaemia	↓	↓	↓	Look for overt/covert loss and replace with appropriate fluid, e.g. saline or blood
Cardiogenic	↓	↓	→↑	Myocardial infarction might need inotropes
Septic	↓	→↓	→↓	Look for source, give antimicrobials ± inotropes if hypotensive

Table 9.5 Fluid replacement

	Na ⁺ (mmol/L)	K ⁺ (mmol/L)	HCO ₃ or equivalent (mmol/L)	Cl ⁻ (mmol/L)	Ca ²⁺ (mmol/L)	Indication (see below)
Normal plasma values	142	4.5	26	103	2.5	
Sodium chloride 0.9%	150	-	-	150	-	1
Sodium chloride 0.18% + glucose 4%	30	-	-	30	-	2
Glucose 5% + potassium chloride 0.3%	-	40	-	40	-	3
Sodium bicarbonate 1.26%	150	-	150	-	-	4
Compound sodium lactate (Hartmann's)	131	5	29	111	2	5

1. Volume expansion in hypovolaemic patients. Rarely to maintain fluid balance when there are large losses of sodium. The sodium (150 mmol) is greater than plasma and hypernatraemia can result. It is often necessary to add KCl 20–40 mmol/L.
2. Maintenance of fluid balance in normovolaemic, normonatraemic patients.
3. To replace water. Can be given with or without potassium chloride. May be alternated with 0.9% saline as an alternative to (2).
4. For volume expansion in hypovolaemic, acidotic patients alternating with (1). Occasionally for maintenance of fluid balance combined with (2) in salt-wasting, acidotic patients.
5. Used for maintenance of fluid balance after surgery. The potassium content may be dangerous in renal failure but occasionally useful in the diuretic phase of acute tubular necrosis where hypokalaemia occurs.

Modified from Kumar and Clark *Clinical Medicine* 8th edn, 2012.

Other actions

- U&Es
- Stop potentially nephrotoxic drugs
- Stop anti-hypertensive drugs
- Ask nurses to record daily weights and to make careful note of fluid intake and urine output on the fluid chart.

Still no urine?

- Are you certain the patient is adequately fluid replete?
- Check that the urine catheter is not blocked or misplaced.
- Give a loop diuretic, e.g. furosemide.
- The patient might now have established acute kidney injury. Refer to nephrologist.

Fortunately this man responded to fluid replacement and produced urine, initially 50 mL/hour.

Key points

- Don't miss urine retention.
- Recognise shock.
- Assess fluid status regularly.
- Most cases will need fluid replacement, and failure to achieve this can result in established renal failure.

ACUTE HEART FAILURE

Acute heart failure occurs when cardiac function falls, causing elevated cardiac filling pressure. This causes severe breathlessness with fluid accumulating in the interstitial and alveolar spaces of the lung (pulmonary oedema).

Case history

A 65-year-old, 50-kg woman who smokes 20 cigarettes per day and with a past history of intermittent claudication, presented to A&E with acute shortness of breath. She is on no medication.

On examination she was centrally and peripherally cyanosed, and peripherally cold and clammy, with a raised JVP, gallop rhythm and bilateral coarse crackles up to both mid-zones. She had absent foot pulses and bilateral femoral bruits. Her BP at presentation was 195/98.

Her ECG showed hypertensive changes (with left ventricular hypertrophy) and a CXR showed bilateral perihilar shadowing. Initially, her biochemistry was:

- Na: 142 mmol/L
- K: 3.1 mmol/L
- Urea: 12 mmol/L
- Creatinine: 115 μ mol/L. eGFR 44 mL/min/1.73 m².

- **Diagnosis:** Flash pulmonary oedema.

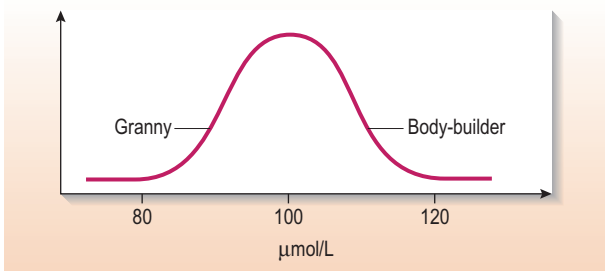


Figure 9.4 Interpreting serum creatinine. The serum creatinine in the healthy population is normally distributed according to muscle bulk. Only large, well-muscled men will usually have a creatinine > 110 if their renal function is normal. Therefore, for small people, creatinine does not get into the 'abnormal' range until half their renal function has been lost.

Treatment

She responded well to oxygen, IV morphine 10 mg, IV furosemide 50 mg and a vasodilator (captopril 12.5 mg) but 4 days later her biochemistry was:

- Na: 142 mmol/L
- K: 6.0 mmol/L
- Urea: 54 mmol/L
- Creatinine: 500 $\mu\text{mol/L}$ (Fig. 9.4). eGFR 8 mL/min/1.73 m^2 .

What has gone wrong?

It is very likely that she has developed acute kidney injury. This is because she has underlying renovascular disease.

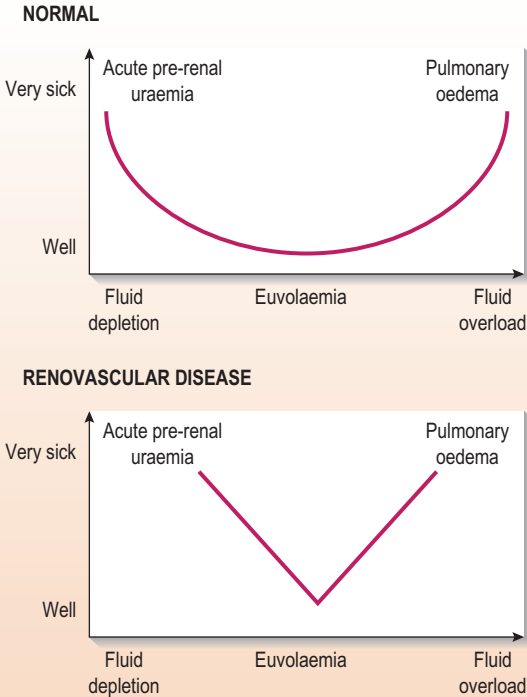
RIFLE criteria for acute kidney injury

Grade	GFR Criteria	UO Criteria
Risk	SCr $\times 1.5$ or GFR decrease >25% (within 48 hr)	UO < 0.5 mL/kg/h $\times 6$ h
Injury	SCr $\times 2$ or GFR decrease >50%	UO < 0.5 mL/kg/h $\times 12$ h
Failure	SCr $\times 3$, GFR decrease >75%, SCr > 350 $\mu\text{mol/L}$ with an acute rise > 40 $\mu\text{mol/L}$	UO < 0.3 mL/kg/h $\times 24$ h
Loss	Persistent AKI > 4 weeks	
ESKD	Persistent ESKD > 3 months	

SCr = serum creatinine; UO = Urinary output; ESKD = end stage kidney disease.

(Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; **380**: 756–766.

There is a new consensus definition that merges RIFLE criteria and the Acute Kidney Injury network definition (Kidney Disease Improving Global Outcomes (K-DIGO) group 2012).



Patients with renovascular disease (who also often have a stiff, non-compliant left ventricle) will develop acute kidney injury or LVF rapidly in the face of mild depletion or overload

Figure 9.5 Fluid status in normal and renovascular disease.

Clinical suspicion of renovascular disease

- Most patients will have disseminated atheroma with missing pulses and/or bruits and a history of smoking.
- Abdominal/renal bruits (although they have a very strong association with renal artery stenosis (RAS)) are rare.
- 'Flash pulmonary oedema' (without an obvious precipitant) is a good predictor of renovascular disease.
- Brittle response to volume loading or off-loading (Fig. 9.5).

Note: her renal function was abnormal at presentation.

ACE inhibitors can cause acute kidney injury in patients with renovascular disease (Fig. 9.6).

How should patients like this be managed?

The key to successful management is very careful fluid control.

Managing acute heart failure (AHF) in the presence of suspected renovascular disease

- Treat the pulmonary oedema: it is a dangerous and very distressing condition.
- Avoid ACEIs/AII blockers: use other vasodilators (this patient was given captopril!).
- Avoid rapid volume off-loading: titrate the diuretic dose against renal function.
- Insert a CVP line and use it properly (see Fig. 9.1).
- Examine (and weigh) the patient regularly: use low-dose dopamine (can be given via peripheral line at 2.5 mg/kg/min) for its natriuretic effect if no response to initial therapy.

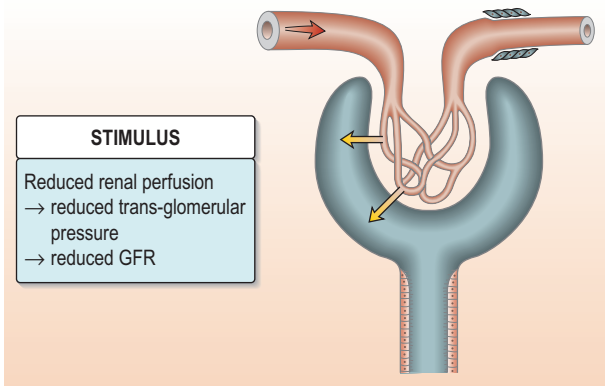
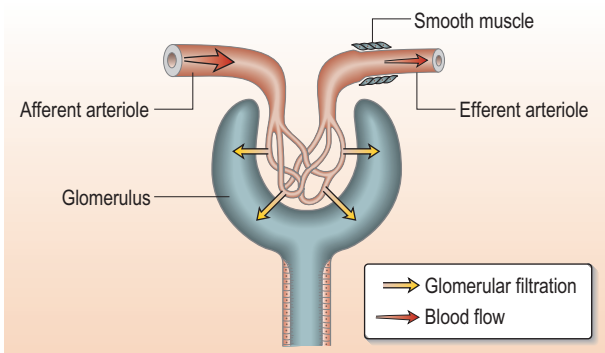
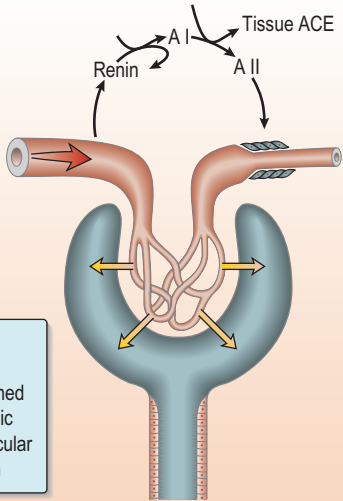


Figure 9.6 Effect of ACE inhibitors/blockers.

RESPONSE
Intra-renal activation of renin/angiotensin system leads to preferential efferent arteriolar vasoconstriction → restores trans-glomerular pressure → restores GFR

Note:
This process may be entirely intra-renal, but once established can spill over into the systemic vasculature. This is how vascular disease causes hypertension



ACE inhibitor (or A II blocker)

ACEIs block this response and can therefore abolish the trans-glomerular pressure gradient, and with it reduction of glomerular filtration

Note:
Although, in this context, blocking angiotensin II leads to decreased renal vascular resistance, any resultant increase in renal blood flow is of no benefit if no glomerular filtrate is generated

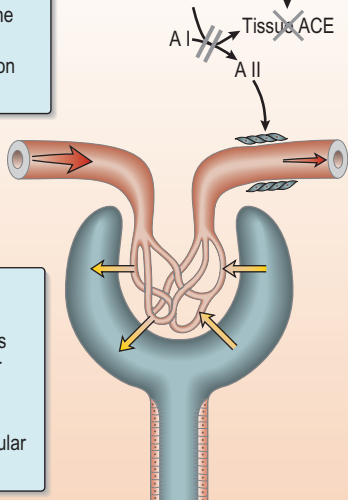


Figure 9.6, cont'd

Renal imaging investigations

- Ultrasound: unequal renal size (> 2 cm difference) is a good predictor of renovascular disease but its absence does not exclude RAS. Duplex ultrasound is used to demonstrate renal artery perfusion.
- Isotope renography: unequal function, slow transit and altered dynamics with captopril are all suggestive of renovascular disease. In experienced hands and with good renal function, its sensitivity and specificity are 70% (creatinine < 150 $\mu\text{mol/L}$); however, in inpatients with severe renal impairment its sensitivity falls below 30%.
- MR angiography is increasingly used to visualise the renal arteries.
- Intra-arterial angiography: the gold standard – should be done by experienced radiologists with minimal contrast load.

Outcome in this patient

She responded to treatment of her AHF, her pulmonary oedema resolved and her renal function returned to normal.

She was then investigated for renal artery stenosis with magnetic resonance angiography showing a narrowing of the right renal artery, thought to be due to atherosclerosis.

She was continued on diuretics and amlodipine, with good control of her blood pressure. She is under regular review.

On the natural history of atheromatous renovascular disease

- ACEI/AII blockers will cause ARF only if both kidneys are affected by RAS, or if only one functioning kidney is present. However, the atheroma is diffuse and progressive. Complete renal artery occlusion with total loss of renal function on one side is usually clinically silent.
- Anatomical renovascular disease is very common and much of it is not physiologically significant (but you can't tell which is which until it is too late).
- Small vessel (intra-renal) disease behaves identically to main renal artery disease (but you can't treat it).

HYPERKALAEMIA

Don't let your patient die tonight!

Case history

A 70-year-old woman has been admitted by the vascular surgeons with an acutely ischaemic lower limb. The right leg, below the knee, was cold, the skin was mottled and there was no pulse below the knee. The patient was in agony with the pain in the limb and she was given intravenous morphine 10 mg. She is on an ACE inhibitor and diuretic for hypertension and also on an NSAID.

It is 2 a.m. The surgical SHO calls you because her K^+ has come back at 7.2 mmol/L. The surgical SHO wants your help.

Remember

- This is a life-threatening condition
- There are no usual symptoms of life-threatening hyperkalaemia.

What do you do next?**As $K^+ > 6.5$ mmol/L:**

- Immediate cardioprotection:
 - 10 mL of 10% Ca gluconate over 10 min.
 - *Note:* action is relatively short lived but dose can be replaced every 15 minutes.
- Get K^+ inside cells: 50 mL of 50% glucose with (or followed by) 10 U insulin. IV 50 mL sodium bicarbonate 8.4% is given over 1 h for severe acidosis $pH < 6.9$. Salbutamol infusion is now rarely used.
 - *Note:* if the patient has a nasogastric tube then put it on free suction because it will remove acid and potassium, causing systemic alkalosis, encouraging influx of potassium intracellularly (Fig. 9.7).

Now you have time to stop and think. The K^+ is telling you that something has gone badly wrong. Find it and treat it!

Common reversible causes of K^+

- Tissue hypoxia/damage
- Acidosis
- K^+ -sparing diuretics
- ACEI
- Blood transfusion
- Acute kidney injury.

Quick and simple ways to stop or reverse underlying causes of raised K^+

- Establish a diuresis.
- Stop ACEIs/NSAIDs.
- Stop blood transfusion.
- Successfully treat systemic sepsis.

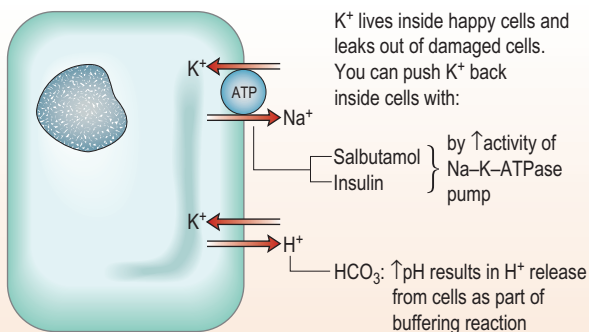
Remember

If K^+ is not responding, your patient might need dialysis – refer to nephrologist. If the patient's early U&Es suggest acute or chronic kidney disease then make arrangements to move the patient to a dialysis unit after initial resuscitative measures.

Don't sit too long on such patients – dialysis could be the only option.

While you are thinking

- Assess volume status.
- Assess ischaemic/damaged tissue. What do the surgeons think about the viability of the leg.



Ca^{2+} – physiological antagonist to effects of extracellular K^+ on the cardiac myocyte

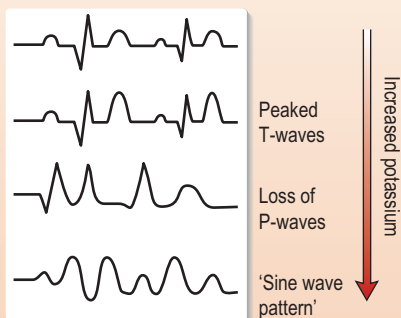


Figure 9.7 Potassium: some facts.

- Repeat ECG.
- Check ABGs.
- Check drug chart.

As you can't promptly reverse the cause

- Give a loop diuretic, e.g. furosemide.
- Treat tomorrow's K^+ with Ca^{2+} resonium (15 g orally with 10 mL lactulose or 30 g PR).

Remember

1 mL of 8.4% $NaHCO_3 = 1$ mmol Na^+ . Don't kill your patient with sodium overload (see Fig. 9.1).

Now go back to re-examine the patient and assess

- Fluid status
- Peripheral perfusion
- Acid-base status
- Re-check U&Es
- ECG changes.

Remember

These myths are NOT true:

- A normal ECG implies your patient is not in danger
- Ca^{2+} resonium will alter tonight's K^+ .

Further management

An urgent angiogram was performed which showed a thrombosis in the right femoral artery near the junction of the popliteal artery.

Thrombolysis was initially used as the surgeons felt removal of the thrombus would not be feasible. She did not respond and gangrene occurred so that a below knee amputation then became necessary.

Less common causes of hyperkalaemia

- Endocrine:
 - Addison's disease
 - Isolated hypoaldosteronism
 - C-21 hydroxylase deficiency
 - Congenital adrenal syndromes, e.g. 3- β hydroxydehydrogenase deficiency.
- Additional drugs:
 - Ciclosporin
 - Succinylcholine
 - NSAIDs.
- Others:
 - Tumour lysis syndrome
 - Periodic hyperkalaemia paralysis
 - Malignant hyperthermia
 - Familial hyperkalaemia acidosis.

THE ACIDOTIC PATIENT

Case history

A 50-year-old woman with chronic kidney disease developed laryngeal oedema as an idiosyncratic reaction to a phenothiazine. She became hypotensive and oliguric. On admission, her blood gases showed:

Continued

Case history (continued)

- pH: 6.9 (Fig. 9.8)
- pO_2 : 6.0
- pCO_2 : 8.2
- HCO_3 : 15

Following intubation, ventilation and fluid resuscitation, her BP rose to 145/70. Her blood gases returned to normal over the next 12 h.

Remember

Only <5% of patients admitted with pH 7.0 or less survive to discharge from hospital. This is because severe acidosis is usually a reflection of serious underlying problems.

How to manage severe acidosis

- Airway
- Breathing
- Circulation.

Problems with any of these will contribute to acidosis and must be corrected.

Identify and treat the underlying problem

Tissue damage/hypoxia is by far the most common cause of metabolic acidosis due to lactic acidosis. Examples include:

- Remember pH is a log scale. A pH of <7.15 means that the $[H^+]$ (hydrogen ion concentration) has doubled.
- Before pH falls significantly, extensive buffering capacity must be consumed. Once this has happened patients are highly unstable.

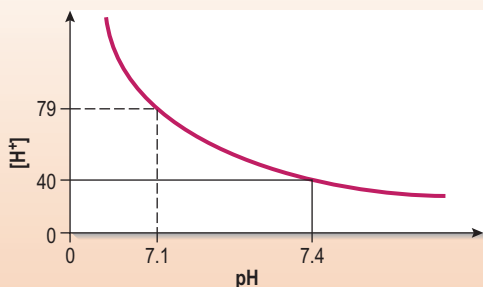


Figure 9.8 pH: some facts.

- Sepsis:
 - Hypotensive patient with warm peripheries
 - Often afebrile and/or normal WBC on presentation especially if very sick or elderly
 - Sometimes develop low PO_4 .
- Rhabdomyolysis:
 - Areas of muscle necrosis not always clinically evident
 - $\text{PO}_4 \uparrow$, $\text{K}^+ \uparrow$
 - Might have a biphasic Ca^{2+} pattern (initially this \downarrow due to binding to damaged muscle, then \uparrow).
- Bowel ischaemia:
 - Severe acidosis
 - $\text{PO}_4 \uparrow$, $\text{K}^+ \uparrow$
 - Often have evidence of peripheral vascular disease.
- Heart failure:
 - Pump failure leading to tissue hypoperfusion
 - Often accompanied by renal hypoperfusion and impaired renal function.
- Overproduction of acid or inability to excrete acid: Examples include:
 - Diabetic ketoacidosis
 - Renal failure
 - Alcoholic ketoacidosis
 - Salicylate intoxication
 - Methanol poisoning
 - Ethylene glycol ingestion.

Note: all the above result in metabolic acidosis with high anionic gap.

Examples of normal anionic gap acidosis (hyperchloraemic acidosis):

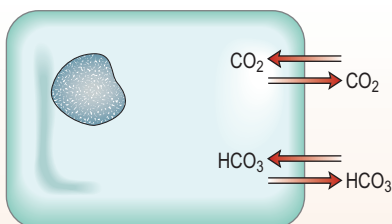
- Diarrhoea
- Renal tubular acidosis
- Dehydration
- Interstitial renal disease
- Uretersigmoidostomy
- Carbonic anhydrase inhibitors (acetazolamide)
- Arginine hydrochloride ingestion
- Ammonium chloride ingestion.

Remember

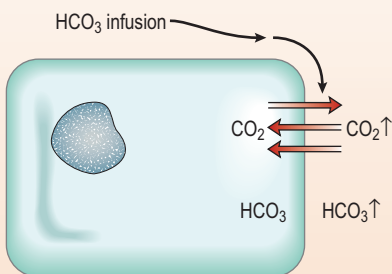
Find and treat the underlying cause.

The role of IV HCO_3 in acidosis

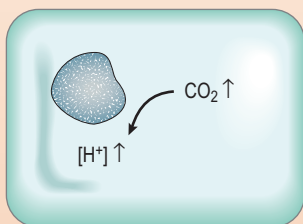
- The role of IV HCO_3 is not clear (Fig. 9.9)!
- Remember, 8.4% $\text{HCO}_3 = 1 \text{ mmol/mL Na}^+$. It is very easy to precipitate volume overload.
- HCO_3 might be indicated if $\text{pH} < 7.25$ in an attempt to reduce the depression of myocardial function produced by severe acidosis.



CO_2 equilibrated more rapidly between ECF and ICF than HCO_3^-



HCO_3^- infusion titrates extracellular H^+ causing a rise in CO_2 which equilibrates across ECF/ICF before the HCO_3^- can get into cells



Intracellular CO_2 rises, leading to worsening intracellular acidosis

Figure 9.9 Theoretical reasons for adverse effect of HCO_3^- in small rodent models of lactic acidosis. Conclusions: if you are called to A&E to see a rat with lactic acidosis, do not under any circumstances give it IV NaHCO_3 .

Remember

Bicarbonate will not save your patient if you don't correct the underlying cause of acidosis (but it might help keep them alive until you do).

ACUTE KIDNEY INJURY

Acute kidney injury is an abrupt deterioration of renal function over the course of a few days or weeks. It is usually (but not always) reversible.

Case history

A 75-year-old man has a 5-day history of anorexia, nausea, vomiting and lethargy. His doctor has noted the following findings:

- Hb: 100 g/L
- Urea: 48 mmol/L
- Creatinine: 820 $\mu\text{mol/L}$. eGFR 6 mL/min/1.73 m². K⁺ 5.6 mmol/L.

The previous history includes mild hypertension and osteoarthritis.

What are your priorities?

1. Safety

- Treat his life-threatening hyperkalaemia (see p. 239).
- Fluid assessment (see Fig. 9.1):
 - Dry: treat with fluids
 - Wet: treat with fluid restriction
 - OK.

In this case, the patient has a K⁺ of 5.6 mmol/L and his fluid status is OK. At this stage, review/stop any drug therapy. Now, you have to consider:

- Why does this man have acute kidney injury?
- Is it reversible?
- Do you need to refer to a renal unit?

2. Test the urine (and send MSU)

Blood + protein = 'active' urine, suggests active glomerular disease in the absence of infection. Some hospitals provide a facility for urinary RBC morphology on fresh urine by polarising microscopy. Predominant dysmorphic RBCs are highly suggestive of glomerular pathology.

Investigations

- Ultrasound (see below)
- Immunological markers: ANA, ENA, ANCA, anti-GBM antibodies, cryoglobulins, complements, ASOT
- Serum protein electrophoresis
- 24-h urinary protein loss

3. Renal tract imaging

In this case the renal ultrasound is normal. This tells you:

- There is a low probability of obstruction
- There is the potential that there is a reversible component.

4. Refer to a renal unit

- Don't delay! The most common concern expressed by renal units is that referring teams wait too long to transfer cases and patients are in a critical condition when they arrive on the unit.
- Be prepared: see Questions you will be asked (below).

Guide to indications for dialysis

There is no magic level of urea or creatinine. Dialysis is indicated:

- In uncontrolled hyperkalaemia
- In unresponsive pulmonary oedema
- When patient symptoms demand.

Outcome

In this case, the patient turned out to be taking an NSAID. He required haemodialysis for uncontrolled vomiting and subsequently had a renal biopsy. This showed tubulo-interstitial nephritis secondary to NSAID therapy. He responded well to a short course of steroids.

Questions you will be asked when referring to a renal unit

- Is the patient passing urine?
- What is the fluid status of the patient?
- Have you done a renal ultrasound?
- Is the urine 'active'?
- Any nephrotoxic drugs?
- Hepatitis status?
- Any information on patient's prior renal function?

Renal tract imaging

Ultrasound

- Non-invasive
- Independent of renal function
- Can measure size (renal length and cortical thickening)
- Limited or no view of ureters
- Low detection rate of renal calculi
- Operator dependent
- CT KUB

Intravenous urogram (IVU)

- Good visualisation of pelvico-calyceal system and ureters
- Gives some functional information

CHRONIC KIDNEY DISEASE

Chronic kidney disease is used to describe long-standing, usually progressive, impairment in renal function.

Case history

A 35-year-old woman registers with a new doctor and is found to be hypertensive (180/105), with blood and protein in her urine. She has no specific symptoms.

On examination pallor, BP 180/105, grade II hypertensive, retinopathy, renal ultrasound – small non-obstructive kidney.

Investigations

- Hb: 85 g/L
- Urea: 18.0 mmol/L
- Creatinine: 310 $\mu\text{mol/L}$, eGFR = 20 mL/min/1.73 m^2 .

Estimation of creatinine clearance

Cockcroft–Gault equation

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times (\text{constant})}{\text{Serum creatinine } [\mu\text{mol/L}]}$$

Constant = 1.23 for males and 1.04 for women.

Modification of diet in renal disease (MDRD) equation

Calculation of estimated GFR by 4 variables:

Estimated GFR (mL/min/1.73 m^2) = $186 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times \text{constant}$ (0.742 if female) \times (1.210 if Black African)

To convert creatinine values in $\mu\text{mol/L}$ to mg/dL multiply by 0.0113.

From: MacGregor MS, Boag DE, Innes A. Chronic kidney disease. *Quarterly Journal of Medicine* 2006; **99**: 365–375.

Clinical features seen in CKD are shown in [Figure 9.10](#).

This woman has irreversible chronic kidney disease and subsequent follow-up showed a progressive rise in creatinine.

Classification of CKD

Stage	GFR (mL/min/1.73 m^2)	Description
1	≥ 90	Normal or increased glomerular filtration rate (GFR), with other evidence of kidney damage
2	60–89	Slight decrease in GFR with other evidence of kidney damage
3A	45–59	Moderate decrease in GFR with or without other evidence of kidney damage
3B	30–44	Moderate decrease in GFR with or without other evidence of kidney damage

Continued

Classification of CKD (continued)

Stage	GFR (mL/min/ 1.73 m ²)	Description
4	15–29	Severe decrease in GFR with or without other evidence of kidney damage
5	<15	Established renal failure

Note: The suffix 'P' can be applied to the stage of CKD if the patient has significant proteinuria, defined as a urinary albumin:creatinine ratio >65 mg/mmol or protein:creatinine ratio >100 mg/mmol.

Source: NICE Clinical guidance 73. Chronic kidney disease. 2011.

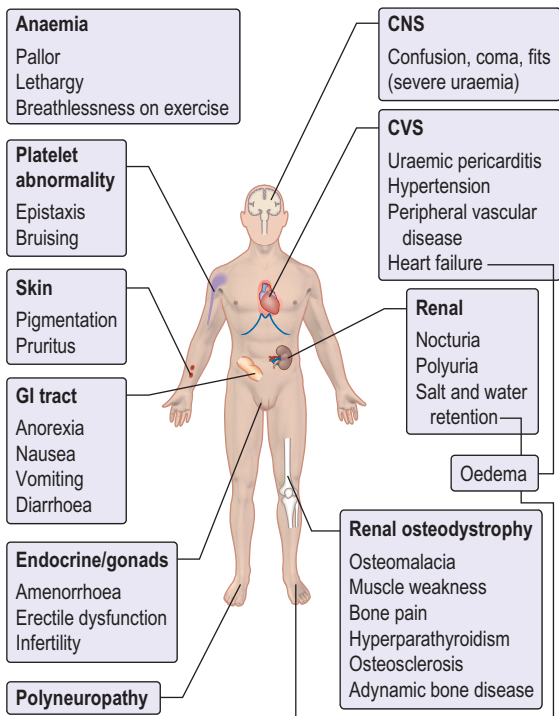


Figure 9.10 Symptoms and signs of chronic kidney disease. From Kumar and Clark Clinical Medicine 8th edn, 2012.

Note: Not all patients with CKD have small, shrunken kidneys. Normal or larger than normal kidneys can be seen in diabetic nephropathy, amyloidosis, polycystic kidneys and hydronephrosis (here cortical thinning is the sign of irreversibility).

How do you manage this case?

Remember

Control of hypertension is the single most useful factor in CKD.

- The approach should be multidisciplinary (Fig. 9.11).

Remember

- CKD is an insidious condition with no specific symptoms. In some cases, patients do not present until they have reached the stage when dialysis is required
- Preparing the patient for dialysis is a specialist task: refer!
- CKD is a major cardiovascular risk factor: the average dialysis patient is approximately 20 times at risk.

Preparing the patient

- Educate: a specialist counsellor should be consulted.
- Renoprotection.

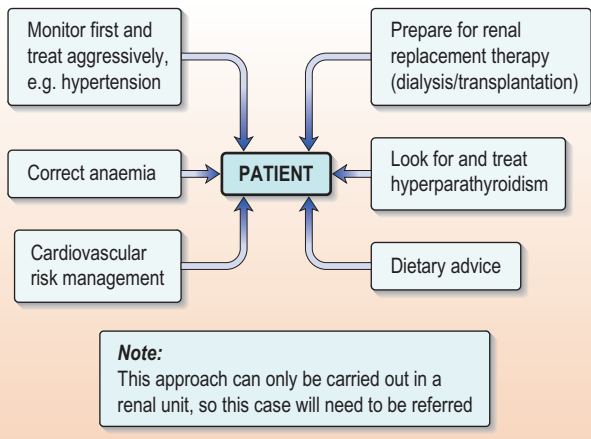


Figure 9.11 Multidisciplinary approach to chronic kidney disease.

Renoprotection

Goals of treatment

BP < 120/80

Proteinuria < 0.3 g/24 hours

Treatment

Patients with chronic kidney disease (CKD) and proteinuria > 1 g/24 hours:

- ACE inhibitor increasing to maximum dose
- Add angiotensin receptor antagonist if goals are not achieved*
- Add diuretic to prevent hyperkalaemia and help to control BP
- Add calcium-channel blocker (verapamil or diltiazem) if goals not achieved

Additional measures

- Statins to lower cholesterol to < 4.5 mmol/L
- Stop smoking (threefold higher rate of deterioration in CKD, if smoker)
- Treat diabetes (HbA1c < 7%/53 mmol/mol)
- Normal protein diet (0.8–1 g/kg bodyweight)

*In type 2 diabetes start with angiotensin receptor antagonist.

- Decide on mode of therapy: haemodialysis versus peritoneal dialysis versus pre-emptive renal transplantation if a live related or spousal kidney donor is willing to donate.
- Plan access surgery: an AV fistula requires at least 6 weeks before it can be used.

Specific conditions:**Hyperparathyroidism**

- Measure PTH: radiographs only become diagnostic in advanced cases.
- Control phosphate:
 - Dietitian
 - Phosphate-binding drugs, e.g. calcium carbonate, calcium acetate, Sevelamer and aluminium hydroxide in selected cases.
- Vitamin D analogues (e.g. alphacalcidol).
- Monitor Ca²⁺, phosphate, PTH and alkaline phosphate levels.

Anaemia

- Correct iron deficiency (if present).
- Erythropoietin: can only be given by IV or by subcutaneous injection × 1 to × 3 weekly. Erythropoietin alpha can only be given by IV route because of increased risk of pure red cell aplasia (PRCA).
- Target Hb 115–130 g/L.
- Monitor BP.

In summary, this woman with CKD had well controlled BP but her renal function gradually deteriorated and she eventually agreed to have haemodialysis and possible transplantation in the future.

Further reading

- Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012; **379**: 165–180.
- Appel LJ, Wright JT Jr, Greene T et al. Intensive blood pressure control in hypertensive chronic kidney disease. *New Engl J Med* 2010; **363**: 918–929.

MULTISYSTEM VASCULITIS/ACUTE GLOMERULONEPHRITIS

Case history

A 54-year-old man with a 1-month history of cough and shortness of breath (SOB), which has not responded to two courses of antibiotics from his doctor (amoxicillin, then clarithromycin and co-amoxiclav), re-presented to his doctor complaining of fatigue, muscle aches and pains. He requested a 'tonic'.

A week later he came to A&E complaining of acute SOB. His CXR showed fluffy bilateral patchy alveolar shadowing, and his serum creatinine was 350 $\mu\text{mol/L}$. On further investigation, he was c-ANCA positive. Renal biopsy showed focal necrotising glomerulonephritis. He responded well to immunosuppression with corticosteroids and cyclophosphamide.

Information

Most doctors see many patients with vague muscular aches and pains in a working day; they will see few, if any, patients with multi-system vasculitis in their working lifetimes.

To identify patients with multi-system vasculitis, dipstick the urine and don't ignore microscopic haematuria.

Inflammatory autoimmune vasculitis: microscopic polyangiitis/Wegener's granulomatosis

Very non-specific presentation – typically vague arthralgia and myalgia with fatigue, anorexia and malaise. At a later stage, patients might develop:

- Vasculitic rash
- Mono-neuritis multiplex
- Arthritis
- Ear/nose/throat symptoms, such as epistaxis or deafness.

At this point the diagnosis is more obvious but these diseases respond well to treatment if diagnosed early.

Remember

If diagnosed late, these diseases have difficult and life-threatening complications.

Pulmonary haemorrhage

- Most common disease-related cause of death in ANCA +ve vasculitis and anti-GBM (glomerular basement membrane) disease (Goodpasture's syndrome).
- CXR appearances very variable but usually patchy alveolar shadowing (can mimic, or be accompanied by, pulmonary oedema or chest infection).
- Often precipitated by pulmonary oedema/infection/smoking.
- Can be diagnosed non-invasively by finding increased KCO (carbon monoxide (CO) binds to blood and gives falsely elevated KCO).

What to do

- The patient requires an urgent nephrology and ITU referral: these patients can become very sick very quickly, and may need ventilation and plasma exchange.

How to diagnose multi-system vasculitis

If you find microscopic haematuria in a patient with non-specific malaise/myalgia:

- Enquire specifically for suggestive symptoms:
 - Nasal congestion/nose bleeds with polyangiitis (Wegener's granulomatosis)
 - Rash
 - Neurological symptoms.
- Examine carefully for:
 - Splinter haemorrhages
 - Nail-fold infarcts
 - Mouth ulcers
 - Rash
 - Neuropathy.
- Don't assume that microscopic haematuria is due to UTI: send an MSU.
- If there are suggestive symptoms or signs: discuss with a nephrologist.
- If there are no suggestive symptoms or signs but MSU is -ve for a urinary tract infection: Check renal function; if it is abnormal, discuss with a nephrologist.

ANCA points (Fig. 9.12)

- False +ves occur in situations of polyclonal B-cell activation (usually on immunohistology but not against specific target antigens).
- ANCA -ve small vessel vasculitis can be clinically and pathologically identical to ANCA +ve vasculitis.
- Changes in antibody titre might be unrelated to, lag behind or precede changes in disease activity in different patients.
- ANCA subtypes are being recognised.

Remember

These diseases will irretrievably damage your patient's kidneys in a matter of weeks. Prompt diagnoses and treatment can make the long-term difference between life on dialysis and life on a small dose of steroids.

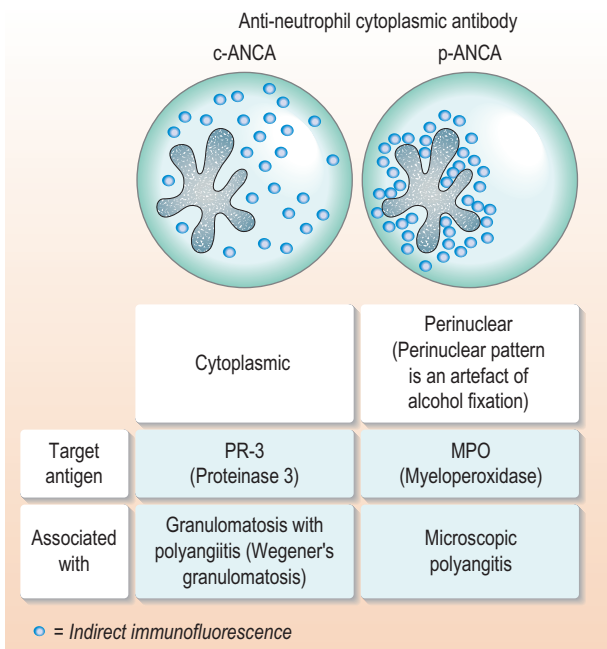


Figure 9.12 Anti-neutrophil cytoplasmic antibody.

Other markers of disease activity

↑ ESR, ↑ CRP, thrombocytosis.

Other rapidly progressive glomerulonephritides (GN)

- Goodpasture's disease is rare: it is classically described as a 'one-hit' disease and is less likely to be preceded by a non-specific prodrome than ANCA +ve vasculitis.
- IgA nephropathy, mesangiocapillary GN due to cryoglobulins, and diffuse proliferative GN in SLE can all present with a rapidly progressive, crescentic nephritis.

Further reading

Berden AE, Ferrario F, Hagen EC et al. Histopathological classification of ANCA-associated glomerulonephritis. *JASN* 2010; **21**: 1628-1636.

INTERCURRENT ILLNESS IN DIALYSIS AND TRANSPLANT PATIENTS

Case history (1)

A 72-year-old, type 2 diabetic, haemodialysis patient was brought in by urgent ambulance to the A&E department complaining of chest pain and shortness of breath. He was due to be dialysed later that day at the nearest renal unit (5 miles away).

On admission he had signs of mild biventricular heart failure with a tachycardia, raised venous pressure, gallop rhythm, basal crackles and peripheral oedema. His ECG showed lateral ischaemia and his Hb was 82 g/L.

He was given IV nitrates and 2 units blood under cover of 40 mg furosemide. As the second unit of blood ran through, he complained of acute shortness of breath, then suffered a cardiorespiratory arrest, from which he could not be resuscitated.

Remember

- Don't give blood transfusion in a dialysis patient unless a nephrologist tells you to – you could precipitate lethal hyperkalaemia and volume overload (and the normal methods of treating these complaints will be ineffective)
- Also: even if your patient survives, you might sensitise him or her to HLA antigens in the blood, thereby denying the chance of a renal transplant
- As a general rule: dialysis patients should not be transfused while on dialysis.

Other things not to do in dialysis patients

1. Access preservation

Dialysis access is essential for life-preserving treatment and potential sites for it are limited and easily damaged irretrievably (Fig. 9.13).

Use veins in hands or feet or the antecubital fossa. For central access use the internal jugular vein.

2. Fluids

Dialysis patients do not need 2 L/day of IV fluid or furosemide postoperatively.

Things to watch out for in dialysis patients

- Vascular disease: ischaemic heart disease is very common in dialysis patients – even young ones. It is often unmasked by anaemia.
- Infection: dialysis patients are significantly functionally immunosuppressed. They cope poorly with sepsis and rapidly become systemically

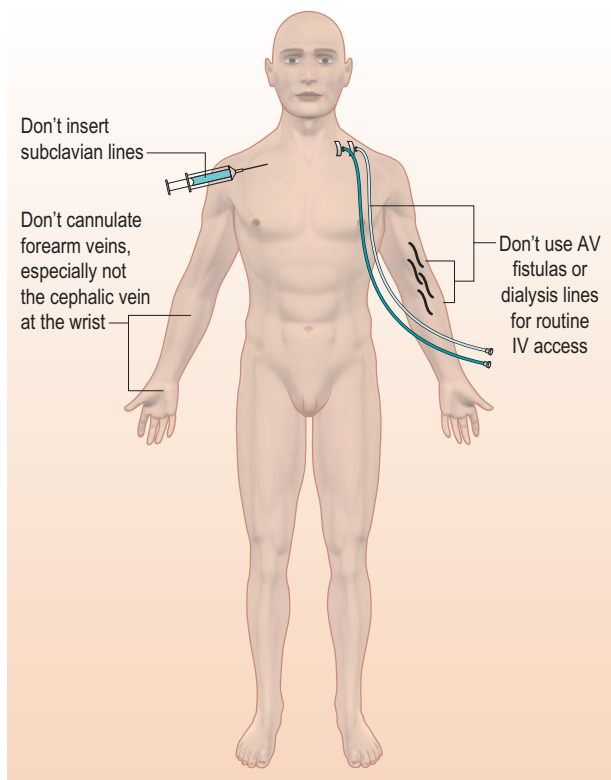


Figure 9.13 Things not to do in dialysis patients.

unwell. Infections in access sites (lines, fistulae, PD catheters) are common and might not be clinically evident, e.g. subacute infective endocarditis and osteomyelitis – always think of these complications.

- Electrolytes: haemodialysis patients are often chronically hyperkalaemic pre-dialysis (and invariably hypokalaemic immediately post-dialysis). They will often present with hypercalcaemia (too much vitamin D or Ca^{2+} -based PO_4 -binders) or hypocalcaemia (too little).
- Poorly compliant patients are routinely hyperphosphataemic; if they then start taking their 'prescribed' doses of vitamin D (1- α calcidol) and Ca^{2+} -based phosphate binders, their $\text{Ca}^{2+} \times \text{PO}_4$ product might exceed 7 mmol/L, precipitating ectopic calcification.

Case history (2)

A 23-year-old renal transplant recipient (primary renal disease was reflux nephropathy), on standard triple-therapy immunosuppression (prednisolone, azathioprine, ciclosporin) presented with a hot, swollen, exquisitely painful right ankle.

The joint was aspirated. The fluid contained 5000 WCC/mm³ with negative birefringent needle-shaped crystals seen on microscopy.

Diagnosis: Gout

The symptoms responded to colchicine 500 µg × 2 daily; allopurinol was started (300 mg × 1 daily) after 4 weeks with continuation of the colchicine therapy.

Three weeks later, the patient presented, shocked with pancytopenia, developed multi-organ failure, and died.

Beware drug interactions that matter in transplantation**Allopurinol and azathioprine**

Azathioprine is metabolised to 6-mercaptopurine, which is metabolised by xanthine oxidase. Allopurinol inhibits xanthine oxidase and effectively trebles or quadruples the functional dose of azathioprine, leading to significant bone-marrow depression.

This was the cause of the man's pancytopenia and multi-organ failure.

Ciclosporin

Increase CyA levels:

- Macrolides e.g. erythromycin
- Calcium channel blockers
- Triazoles.

Reduce ciclosporin levels:

- Rifampicin
- Anti-epileptics.

Things to watch out for in renal transplant patients**Infections**

The level of immunosuppression is high initially, then reduced. A wide range of opportunistic infections can occur (Table 9.6).

Table 9.6 Opportunistic infections that can occur in renal transplant patients

Viral	Bacterial	Protozoal	Fungal
CMV	TB	<i>Toxoplasma</i>	<i>Pneumocystis</i>
EBV	<i>Listeria</i>		<i>Candida</i>
HSV	<i>Nocardia</i>		<i>Aspergillus</i>
VZV	<i>Salmonella</i>		

Vascular disease

Remains very common after transplantation. Death (with a functioning graft) from IHD is the cause of death in 50% of patients.

NEPHROTIC SYNDROME

Nephrotic syndrome is not a diagnosis but a set of signs and symptoms:

- Peripheral oedema
- Proteinuria: usually > 3 g per day
- Hypoalbuminaemia
- Hypercholesterolaemia: this is a secondary phenomenon due to increased liver synthesis associated with increased protein synthesis:
 - It can be very resistant to lipid-lowering drugs
 - Treat the primary condition
- Hypertension, which accompanies the fluid overload
- Thrombophilia: nephrotic syndrome is associated with an increased clotting tendency and risk of thromboembolic disease. It is also a secondary condition. However, while the patient is nephrotic, anticoagulation is indicated, especially in membranous nephropathy.

Remember

In nephrotic syndrome there is a reduction in *relative* circulating volume in the presence of oedema.

Case history

An 18-year-old woman presents with a 2-week history of swollen ankles and mild breathlessness on exertion.

On examination she had dependent oedema of the lower limbs to the knee with some facial oedema. Her pulse was normal, BP 150/90. She had bilateral pleural effusions.

Investigations

- Serum albumin 19 g/L
 - 24-h urine protein 5.6 g per day
 - Fasting cholesterol 8.7 mmol/L
- } confirming the nephrotic syndrome
- Urine analysis, proteinuria, no blood or red cell casts ('Bland' urine segments).

Management

The aim in all such cases is to find the cause.

How?

Although various non-invasive tests might hint at the diagnosis, in most adult cases a renal biopsy is required.

Renal biopsy findings

Don't panic – you do not need to know about renal histopathology!

Table 9.7 Some common diagnoses and therapeutic strategies

Diagnosis	Treatment
Minimal change disease	Steroids (first line) Cyclophosphamide
Membranous nephropathy	None or ACE inhibitors to reduce proteinuria or steroids Alkaloids (cyclophosphamide or chlorambucil) Rituximab
Lupus nephritis	Prednisolone + cyclophosphamide/ mycophenolate
Diabetic nephropathy	ACEI or All receptor antagonist Control hypertension: aim BP < 120/80 Improve glycaemic control
Vasculitis	Prednisolone +/- azathioprine
Amyloid	Treat underlying condition
HIVAN (collapsing FSGS)	Anti-retroviral therapy

FSGS, focal segmental glomerulosclerosis.

Table 9.7 lists some of the common diagnoses and therapeutic strategies.

This patient turns out to have 'minimal change' disease. She responds to oral steroids (60 mg/m² daily) slowly with a significant reduction in urinary protein, only after 12 weeks of high-dose therapy.

Remember HIV-associated nephropathy (HIVAN) in high-risk patients as a cause of unexplained renal impairment. HIV patients can also develop drug nephrotoxicity and haemolytic uraemic syndrome. Modern anti-retroviral therapies have resulted in good renal outcomes in patients with nephrotic syndrome due to HIVAN.

Remember

The use of IV albumin is controversial but its use is declining. However, where severe reduction in circulating volume threatens renal function, it might help prevent acute kidney disease.

Future progress

This woman's steroids were reduced but she subsequently relapsed and was therefore given prednisolone 15 mg daily with cyclophosphamide 2 mg/kg daily for 12 weeks. She is presently in remission.

Further reading

Tervaert TW, Moovaart AL, Amann K et al. Pathological classification of diabetic nephropathy. *JASN* 2010; **21**: 556–563.

HAEMATURIA WITHOUT ALBUMINURIA

Information

- Macroscopic haematuria (red colour urine): can be confused with bile pigments, porphyrins, haemoglobin and myoglobin. Confirm haematuria by microscopy
- Microscopic haematuria: more than 3–5 RBC per HPF on microscopy

Remember

Haematuria cannot cause anaemia. Look for another cause of anaemia such TB, neoplasms, and blood dyscrasias.

Aetiology

- Systemic: fever, anti-coagulant therapy, sickle-cell trait or disease, strenuous exercise or coagulopathies.
- Renal: glomerulonephritis (GN; IgA nephropathy, Alport's, thin basement nephropathy), interstitial tubulonephritis, renal infarcts, TB, polycystic disease, papillary necrosis, neoplasm, trauma, vascular malformations.
- Urinary tract: calculi, foreign bodies, neoplasms, endometriosis, trauma, infections.

History

- Menstrual history to exclude vaginal cause of blood in urine.
- Frequency, urgency, dysuria or urethral discharge suggests bladder or urethral involvement.
- Pain or colic might be seen with stones, obstruction, infarction, polycystic kidney disease (PCKD).
- Bleeding at the beginning of micturition suggests urethral cause whereas terminal bleeding is associated with prostate or bladder pathology.
- Rectal or perineal pain suggests prostatitis.
- Weight loss might suggest a neoplasm.
- History of blood dyscrasia or anti-coagulant therapy: anticoagulant therapy usage and haematuria should be investigated further for underlying lesions of urinary tract.
- Family history of PCK, sickle-cell disease or GN (Alport's or thin basement nephropathy).
- Upper respiratory tract infections or gastroenteritis: suggests exacerbations of IgA nephropathy.

- History of easy bruising or vasculitic rash, arthralgia and abdominal pain suggests Henoch-Schönlein purpura. Occasionally anti-GBM disease, SLE or vasculitis can present as isolated haematuria.

Physical examination:

- Look for elevated blood pressure or oedema (usually implies renal lesion).
- Bilaterally palpable kidneys (PCK).
- Unilateral mass (neoplasm or cystic or hydronephrotic kidney).
- Fever and tenderness over renal angle (pyelonephritis).
- Tender prostate (prostatitis).
- Presence of atrial fibrillation or valvular heart disease suggests embolism or renal infarction.
- Presence of petechiae, ecchymosis, lymphadenopathy or splenomegaly may signal blood dyscrasia or clotting disorder.

Investigations

- Complete urinalysis: polarised microscopy may reveal dysmorphic RBC (glomerular origin) or isomorphic RBC (urothelial origin). Pyuria and haematuria with bacterial growth suggest UTI. No bacteriological growth triggers search for TB
- Full nephritic screen
- Imaging
- Ultrasound scan of kidneys and bladder with residual bladder volume assessment
- IVU/CT: stones and urinary tract lesions can be missed on ultrasound scan alone
- Cystoscopy is the best procedure for evaluating urinary tract after KUB/CT

URINARY TRACT INFECTION (UTI)

Case history

You are called to see a 19-year-old woman in MAU who is complaining of a 2-day history of frequency, dysuria and urgency. She has a temperature of 39.8°C with some right loin pain. Yesterday she had a rigor. She has a **urinary tract infection (UTI)** and presumed acute pyelonephritis in view of her high fever and right loin tenderness.

Information

- **Frequency** is defined as voiding every 2 hours or more than seven times per day. A variety of factors can affect voiding intervals, including fluid intake, drugs (diuretics), alcohol and caffeine. Patients with polyuria from any cause complain of

Information (continued)

frequency with an increased urine flow. By contrast, bladder inflammation can cause frequency without an increase in urine flow.

- **Urgency** is described as powerful sensation to void, regardless of bladder volume. Typically, voided volumes of these patients are small – much less than the patient's normal maximum bladder capacity. Urgency is often caused by bladder inflammation but prostatic enlargement and external compression of the bladder by masses (as in pregnancy) can also generate the feeling of urgency.
- **Dysuria** (painful micturition) suggests irritation or inflammation in the bladder neck or urethra, usually because of bacterial inflammation.

She tells you that this is her first episode of an UTI. She has recently started to have frequent sexual intercourse with a new partner. She has no vaginal discharge and has never had a history of sexually transmitted infections.

Physical examination

A complete physical examination shows no abnormality apart from right loin tenderness. There is no urinary bladder distension or suprapubic tenderness.

Investigations

- Urinary dipstick are positive for both nitrite and leucocyte esterase.
- Urine microscopy: pyuria, bacteriuria and leucocyte casts are consistent with UTI.
- Mid-stream urine specimens sent for culture and sensitivity show *E. Coli* 10^5 organisms/mL.
- Full blood count, serum urea and electrolytes and blood cultures show no abnormality.
- An abdominal ultrasound showed no abnormality of the right kidney. Ultrasound should be performed when pyelonephritis is suspected to rule out calculi obstruction and incomplete emptying.

How would you manage this patient?

The most common bacterial cause of a UTI is *E. coli*. Administer one of the appropriate broad-spectrum antibiotics intravenously while waiting for culture report; pay specific attention to patient's state of hydration:

- Cefuroxime (750 mg 8-hourly) for 3 days, then switch to oral therapy as per sensitivities
- Ciprofloxacin (500 mg oral \times 2 daily if no sensitivities are available)
- Total antibiotic therapy is for 10 days.

She made a good recovery.

Prophylactic measures to prevent further UTIs were advised:

- A 2 L daily fluid intake
- Voiding at 2- to 3-hour intervals with double micturition if reflux is present
- Voiding before bedtime and after intercourse
- Avoidance of spermicidal jellies and bubble baths and other chemicals in bathwater
- Avoidance of constipation, which may impair bladder emptying.

Further reading

Hooton TM. Uncomplicated urinary tract infection. *N Engl J Med* 2012; **366**: 1028-1037.

RENAL AND URETERIC COLIC

Case history

A 36-year-old man presented to his local A&E with excruciating right flank pain. How will you approach this case?

Likely diagnosis

Renal colic, which is often unilateral, is characterised by excruciating intermittent pain, usually originating in the flank or kidney area, which radiates across the abdomen towards the suprapubic region. The pain of ureteric colic has similar characteristics but typically radiates along the course of the ureter, frequently into the region of the genitalia and inner thigh.

Aetiology

- Renal colic is usually caused by stretching of the renal capsule due to acute inflammation or bleeding within the kidney. Acute pyelonephritis, an expanding cyst or an acute expansion of the renal pelvis due to pelviureteric obstruction by calculus or blood clot are the usual causes.
- Ureteric colic is often caused by the passage of a calculus, sloughed papilla or blood clot.
- Renal stones are usually calcium oxalate or calcium phosphate and caused by hypercalcaemic or hyperoxaluric states. Other types of stones are struvite (magnesium ammonium phosphate) stones, which are caused by urea-splitting organisms, cystine stones (the result of an inherited disorder of cystinuria) and urate stones (idiopathic or hyperuricosuric state).

In the history, ask about:

- Pain: this is usually associated with GI symptoms (nausea, vomiting, abdominal distension).
- Chills, fevers and increased frequency are common.
- Age at which symptoms of stones were first noted.
- Family history of nephrolithiasis.

- History of fractures or prolonged immobilization.
- Previous urinary infections or manipulations.
- Intake of milk, alkali, salt and vitamins A, D and C.

Physical examination

The physical examination is usually unremarkable except for the presence of flank tenderness.

How would you investigate this patient?

- Urinalysis: the urine might be normal despite multiple calculi. Macroscopic or microscopic haematuria is common. Pyuria with or without bacteria may be seen.
- CT-KUB (CT of kidney, ureter and bladder) is carried out during the episode of pain; a normal CT excludes the diagnosis of pain due to calculous disease. The CT-KUB appearances in a patient with acute left ureteric obstruction are shown in [Figure 9.14](#).

How would you manage this patient?

Give adequate analgesia, e.g. IV infusion diclofenac 75 mg, repeating as necessary. Opioids can usually be avoided.

This patient passed a small stone later in the day; it was found to be a calcium oxalate stone. He was referred to the renal physician for the cause of his stone formation.

Cause of stone formation

- Urinary excretion of calcium, phosphate, oxalate, urate, cystine should be performed on at least two separate occasions.

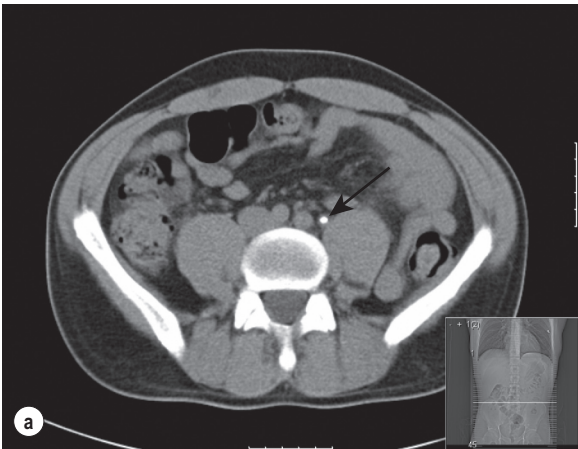


Figure 9.14 (a) Left ureteric calculus.

Continued

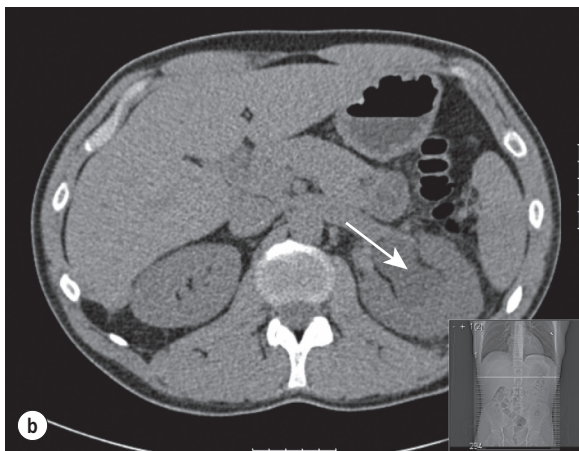


Figure 9.14, cont'd (b) A dilated renal pelvis (arrow) proximal to the ureteric stone in (a).

- Morphological and biochemical analyses should be performed on all the stones that are passed.

This patient was advised to take a high fluid intake and dietary oxalate restriction (refer to a dietitian).

Further reading

Worcester EM, Coe FL. Calcium kidney stones. *New Engl J Med* 2010; **363**: 954–963.

SYNCOPE

Simple faints are a common and benign condition. However, anyone witnessing a faint will know that patients can look awful and it is not surprising that they are often brought to hospital for assessment. Patients who faint are often sat in a chair or even stood up – in both cases causing a recurrence or delaying recovery.

Case history (1)

A 25-year-old man is brought to hospital having fainted at work. He still appears pale but clinical examination is normal. He had a similar episode 2 years earlier. His resting 12-lead ECG is normal.

What are the key questions in establishing the diagnosis?

- Reliable eye-witness account: if not available, make a phone call to the patient's workplace.
- Prodromal symptoms: non-specific but almost always present for some minutes before a vasovagal attack (faint).
- Precipitating cause: anything from the sight of blood to a hangover!
- Circumstance of event, frequently in:
 - Pub (even without alcohol)
 - Restaurant: before or after food
 - Church, mosque or synagogue
 - Warm environment.

In the absence of any abnormal investigations, the most likely **diagnosis is vasovagal syncope** (see Table 15.8, Features of fits and faints). You should be aware of some other specific forms of vasovagal syndrome:

- Carotid sinus syncope: on turning head or shaving the chin. Due to carotid sinus hypersensitivity, usually in the elderly.
- Cough syncope: after a paroxysm of coughing, usually in a patient with obstructive airways disease.
- Micturition syncope: more common in men. Usually occurs in the night when going to pass urine or during micturition itself.

What is the differential diagnosis?

There are many other causes of syncope and all might need to be excluded.

- Cardiac:
 - Arrhythmia: associated with either profound bradycardia or tachycardia. Symptomatic palpitations can be a pointer but are often not present.

- Structural: e.g. outflow obstruction (notably aortic stenosis or hypertrophic cardiomyopathy), ischaemia, tamponade, pulmonary embolism.
- Neurological: seizures, cerebrovascular disease (TIA, CVA or vertebro-basilar ischaemia) are the most common causes. A good eye-witness account is key to the diagnosis. *Note:* Some jerky movements of the limbs, and even incontinence, can occur in a prolonged vasovagal attack, especially if the patient remains upright.
- Metabolic:
 - Hypoglycaemia: well known in diabetics. Spontaneous hypoglycaemia from an insulinoma is a rare cause
 - Hypoxaemia
 - Drugs/alcohol.
- Hyperventilation/anxiety (if suspected, symptoms can often be readily reproduced by voluntary hyperventilation): usually associated with a tachycardia. The patient often has symptomatic palpitations and might feel light-headed, a feeling of being distanced from the surroundings, chest pain and/or paraesthesiae with numbness in arms, hands or lips. Pallor and peripheral cyanosis can be striking in a full-blown attack. Circumstances provoking an attack can often be the same as for a faint (e.g. warm room, stressful situation).
- Orthostatic hypotension: especially in elderly patients. This is often caused by drugs, e.g. for hypertension, but don't forget autonomic neuropathy and Parkinson's disease.

A cardiac cause of syncope should be sought in all patients with known structural heart disease.

- **Progress.** This man was sent home, having made a full recovery from his 'faint'.

Case history (2)

A 68-year-old man passed out suddenly at the wheel of his car and ran into the car in front. His wife reports that he was pale and sweaty but that loss of consciousness was brief and he recovered quickly.

On examination in A&E, pulse 78/min, BP 140/85, no abnormality found on examination.

His ECG showed left bundle branch block (LBBB).

Practice points

- Sudden loss of consciousness without warning must be assumed to be a cardiac arrhythmia until proved otherwise.
- Altered consciousness when driving has important legal implications and the patient must be warned not to drive again until the diagnosis is established.

Investigation

The history of the event is the key to further investigation and blanket investigations are unrewarding without some clinical pointers as to the cause.

Generally, a single faint requires no further investigation but if there is some diagnostic doubt the symptoms can be reproduced by a tilt test. This is usually carried out with a mechanised tilt table giving a head-up tilt of 60° for 45 min, with continuous ECG and BP monitoring. Although false positive results can occur, if the prodrome before the faint reproduces the symptoms it provides strong support for the diagnosis.

This patient required further investigation as the LBBB indicates cardiac disease.

- **Diagnosis.** This man's echocardiogram (echo) showed no abnormality. However, his ambulatory ECG monitoring subsequently showed periods of asymptomatic **Mobitz type II second-degree heart block**.
- **Progress.** A pacemaker was implanted and he had no further problems.

Case history (3)

JR is a 26-year-old physiotherapist. Her first episode of unconsciousness occurred when she was at a party with her medical team. A nursing colleague thought that she was pulseless at the time of the collapse; the possibility of excess alcohol was considered. On arrival in A&E at a nearby hospital she was intubated and ventilated, and kept ventilated overnight. The next day she was well and therefore discharged. She had two further similar episodes requiring overnight admission to hospital.

Investigations

A 12-lead ECG and cardiac enzymes were normal on all three admissions. She was investigated with 24- and 48-h ECG tapes, echo and CT scanning of the head but no abnormalities were found.

An electrophysiological study was therefore performed, to exclude the possibility of tachyarrhythmia. During this study she spontaneously became bradycardic and hypotensive but no arrhythmias were induced.

A tilt table test performed the following day produced profound bradycardia, hypotension and syncope on 60° head-up tilting.

Remember

In a tilt test, syncope is often accompanied by 10–20 s of asystole. This recovers as soon as the patient is returned to the flat; for this reason a doctor should always be present.

Diagnosis

Neurally mediated syndromes are due to a reflex (called Bezold–Jarisch) that may result in both bradycardia (sinus bradycardia, sinus arrest and AV block) and reflex peripheral vasodilatation. These syndromes usually present as syncope or presyncope (dizzy spells).

Treatment and progress

A DDD pacing system (see p. 278) was implanted and programmed to produce a tachycardic response to counter any detected bradycardia of sudden onset. So far she has had no more syncopal attacks.

A CLINICAL APPROACH TO PATIENTS WITH TACHYCARDIA

The main reason people have difficulty assessing tachyarrhythmias is that they concentrate on the ECG changes without thinking about the patient to whom the ECG belongs.

Case history (1)

A 35-year-old man presents with a tachycardia at a rate of 180 per minute. He is not seriously compromised by his tachyarrhythmia and the BP is 128/64. The ECG shows narrow complex tachycardia.

There are three simple questions you need to ask yourself as you approach a patient with an acute tachyarrhythmia:

- 1. What is the heart rate? – i.e. 180 beats/min in this man**
- 2. Has the patient collapsed?**

In other words, is the patient clinically compromised by the tachycardia or not? In assessing the degree of cardiovascular collapse take the heart rate into account. Remember that the maximal heart rate you would expect a patient to achieve on the treadmill is 220 minus age.

Someone with a heart rate at this level (180 bpm) is going at the same rate you would expect if they had just hurried up several flights of stairs.

This man is not compromised by the tachycardia so it is likely that he has a good ventricle. People with heart rates substantially above their predicted maximum who tolerate the situation well are more likely to be suffering from a primary electrophysiological problem than from an arrhythmia secondary to LV disease.

- 3. Are the ECG complexes broad or narrow?**

Divide tachycardias into broad complex (QRS complex of > 120 ms or three small squares on the standard ECG) or narrow complex, rather than try to split them into supraventricular tachycardia (SVT) and ventricular tachycardia (VT) at the first glance. If you follow this approach you will not treat VT as an SVT, which is the error to avoid.

Having answered these questions, you should decide who needs admission to hospital (Table 10.1).

Table 10.1 Patients with tachycardia: who to admit to the Medical Assessment Unit?

	Broad complex	Narrow complex
Collapsed	Usually need immediate cardioversion and must be admitted from A&E. Do <i>not</i> give verapamil or other negatively inotropic drugs	Usually need admission into hospital, especially if the patient is in heart failure
Did not collapse	The most difficult category to sort out	Can probably go home if tachycardia stops on treatment (Case 1)
	Probably need admission to sort out diagnosis	Need outpatient assessment
	Irregular tachycardia in this group may be due to WPW with AF, so do <i>not</i> give verapamil	If this is a recurrent problem they need to be referred to a cardiologist to be considered for EPS, as they may benefit from radiofrequency ablation of their pathway or their arrhythmia focus

AF, atrial fibrillation; EPS, electrophysiological studies; WPW, Wolff–Parkinson–White syndrome.

Take a 12-lead ECG of the arrhythmia: this is essential to sort VT from the SVT. It is also valuable in sorting out the mechanisms in narrow complex tachycardias; the retrograde P waves can be seen in the ST–T segments in re-entrant tachycardias, but they may be seen only in some leads. **Do not be fooled into thinking you can diagnose and manage arrhythmias with rhythm strips alone.**

Remember

Think about the underlying state of the ventricle.

To be safe:

- Always assume a broad complex tachycardia is VT until proved otherwise.
- If in doubt use DC cardioversion rather than drugs.
- Seek advice if your first drug does not work.
- Beware of verapamil (which should not be used as first-line therapy) and other negatively inotropic drugs.
- Check the electrolytes and correct them appropriately before using drugs, but do not delay treatment in a patient who is compromised because you are waiting for results. Remember in an emergency, K⁺ levels can be roughly measured using blood gas machines in A&E and used to guide replacement therapy.

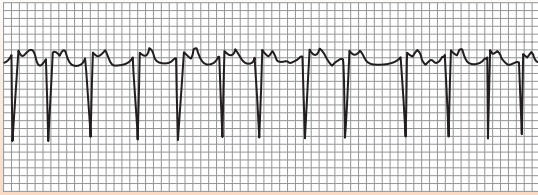


Figure 10.1 Narrow complex tachycardia.

The ECG and classification of tachycardias

Broadly speaking, tachycardias are classified as either supraventricular (SVT) or ventricular (VT) in origin.

SVT

These are narrow complex tachycardias (Fig. 10.1), unless there is bundle branch block. Adenosine is very useful for their diagnosis and will terminate some SVTs:

- Atrial tachycardia: an SVT from a focus in the atrium, rather than due to re-entry.
- Atrial flutter (Afl): look for regular rhythm, often with a rate of 150. Adenosine will help in the diagnosis, often revealing underlying flutter waves.
- Atrial fibrillation (AF): look for lack of P waves, irregular rhythm and baseline; this can be very hard to see with very fast rates, in which case adenosine will help.
- Re-entrant tachycardias:
 - Wolff-Parkinson-White (WPW) is the classic example of a re-entrant tachycardia. The depolarisation wavefront 're-enters' the atrium through the bundle of abnormal conducting tissue between ventricle and atrium. In some cases a bundle is present but is not visible on the resting ECG so that it is a 'concealed pathway'. Never treat AF in WPW with digoxin or verapamil – this can lead to dangerous retrograde conduction down the accessory pathway leading to VF.
 - AV nodal re-entry tachycardia (AVNRT).

Features suggesting that a tachycardia might be an SVT

- Normal LBBB or RBBB morphology but be careful: VT from RV outflow tract with LBBB morphology can look like SVT. A small stubby R wave in V1-2 is characteristic of VT.
- You might be able to see evidence of both atrial and ventricular activity. A constant relationship between the P waves and the QRS complexes suggests a supraventricular origin.
- The frontal and horizontal QRS axes are in the same general direction as that in sinus rhythm.
- It slows with manoeuvres designed to increase vagal tone, e.g. carotid sinus massage.
- If the onset is witnessed you might see a P wave that is premature.
 - **Diagnosis.** Narrow complex supraventricular tachycardia.

Table 10.2 Distinction between supraventricular tachycardia (SVT) with bundle branch block and ventricular tachycardia (VT)

VT is more likely than SVT with bundle branch block where there is:

- a very broad QRS (> 0.14 s)
- extreme left axis deviation
- atrioventricular dissociation
- a bifid, upright QRS with a taller first peak in V_1
- a deep S wave in V_6
- a concordant (same polarity) QRS direction in all chest leads (V_1 – V_6)
- presence of capture or fusion beats
- no response to adenosine

Management

This rhythm responded to adenosine (see below), 3 mg IV going up in 3-mg aliquots to a maximum of 12 mg. Intravenous beta blockade (Esmolol has a very short half-life of seconds and can be very useful) is also used. Synchronised DC cardioversion (start with 50 J) should be used if medication fails.

Case history (2)

A 57-year-old woman presents with a tachycardia at a rate of 132 per minute.

On examination she is hypotensive (90/50), looks pale and distressed and has bibasal crackles.

The 12-lead ECG shows an axis of -120° and the complexes are predominantly positive across the chest leads (regular broad complex tachycardia).

- **Diagnosis.** This is broad complex tachycardia with gross axis deviation, probably VT (see Table 10.2). She needs urgent treatment (see below).

Ventricular tachycardia (VT)

This causes a broad complex regular tachycardia (Fig. 10.2), often called monomorphic VT. However, a broad complex pattern can be caused by any tachycardia if there is a pre-existing abnormality of the conduction system (usually bundle branch block). So, for example, AF with bundle branch block can cause a broad complex tachycardia that is irregular. Although adenosine (see below) can be useful for diagnostic purposes, do not waste time using it if the patient is compromised.

Features suggesting that a tachycardia might be a VT

- A **QRS duration** of > 140 ms strongly suggests a ventricular origin.
- The frontal and horizontal **axes** are grossly discordant with that seen in sinus rhythm. Most people are used to looking at the frontal QRS axis in the limb leads. The horizontal axis is estimated by seeing where the predominantly negative QRS complexes become equiphasic as you look

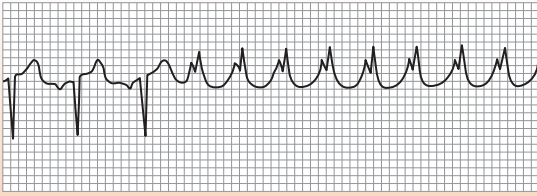


Figure 10.2 Broad complex tachycardia after three normal beats.

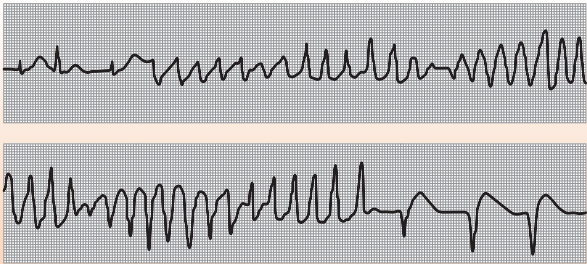


Figure 10.3 Torsade de pointes showing the complexes twisting around the baseline.

across from V1 towards V6. This equiphasic point is called the zone of transition and is usually at V3 or V4. In VT there might be no transition zone or it might be far to the right, or left, of V4.

- **QRS morphology:** the pattern is not typical of LBBB or RBBB. These are specific appearances that strongly suggest VT, e.g. concordance; seek help if unsure.
- **Fusion beats:** these are beats where there is simultaneous activation of the ventricles from a focus of arrhythmia and from the atria via the AV node at the same time. These beats will look like a cross between the standard VT complex and the patient's normal complexes in sinus rhythm.
- **Capture beats:** occasionally the atria 'captures' a normal complex in the midst of a tachycardia.
- You might be able to see evidence of both atrial and ventricular activity. If there is no constant relationship between the P waves and the QRS complexes it suggests a ventricular origin and this is called atrioventricular dissociation.

A word about torsade de pointes

Torsade de pointes is an uncommon form of VT with a characteristic ECG pattern (often called polymorphic VT (Fig. 10.3)). The complexes appear to twist around the baseline by virtue of their changes in amplitude. It is particularly associated with syndromes involving a long QT interval.

Correct diagnosis of torsade de pointes is necessary because the treatment is very different from VT and treating the underlying cause can often have a marked effect.

The acute treatment of arrhythmias

Remember

Always think about the underlying state of the ventricle when treating an acute arrhythmia.

Problems with the use of any anti-arrhythmic drugs:

- Many arrhythmias arise as a result of pre-existing LV disease. You need to be aware of any drugs that you give which could further suppress LV function and make matters worse.
- A drug that is ineffective for the rhythm in question might also depress ventricular function without alleviating the rate-related stress on the ventricle.
- The final catch when you are treating arrhythmias with drugs (Fig. 10.4) is that ischaemia might alter the electrophysiological activity of drugs. This means that drugs that are anti-arrhythmic under normal circumstances become pro-arrhythmic in ischaemic myocardium.

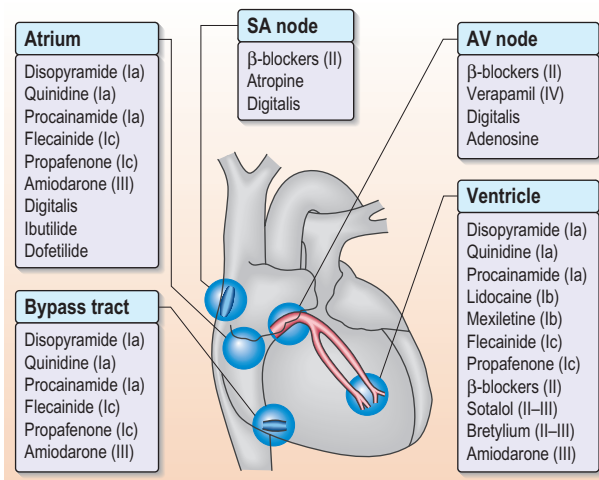


Figure 10.4 Drugs used to treat arrhythmias. The numbers in brackets refer to the Vaughan-Williams classification.

This limits the use of drugs in many patients because it is often difficult to exclude the possibility of coexisting ischaemia. Because of these problems it is often safer to use DC cardioversion than drugs.

Remember

Both digoxin and verapamil can be dangerous in WPW; if uncertain it is safer to cardiovert.

A word on adenosine

Intravenous adenosine has revolutionised the diagnosis and management of acute tachycardias. It should be used in most SVTs and is safe because of its very short half-life. The major limitation is that it should not be used in asthmatics. It will not usually cardiovert AF or flutter but will slow the rate transiently (often for only one or two complexes – have the ECG running) and enable you to see the baseline, helping you make the diagnosis. It will cardiovert most other SVTs. Although it is safe to give adenosine to patients in VT, it will not usually cardiovert the problem, although it might slow the rate. Remember to give it as a rapid bolus, warn the patient he or she will feel *terrible* transiently and remember that he or she might become transiently asystolic.

Management of this patient (Case 2)

This patient has a ventricular tachycardia with severe hypotension and pulmonary oedema. She requires emergency DC cardioversion. Measure and correct any electrolyte abnormality while preparing for DC cardioversion. If in doubt, give empirical intravenous magnesium sulphate, 8 mmol over 10–15 min (it is not appropriate to give K^+ because hypo- or hyperkalaemia can be arrhythmogenic, so you must know serum K^+ before treating it). The arrhythmia did not settle with the DC shock, and IV amiodarone was started with a view to repeat DC cardioversion.

This patient has clinical evidence of poor LV function but in a patient who has a good LV, a beta blocker such as sotalol might be used. Finally, in patients refractory to treatment, remember the possibility of torsade de pointes, with low magnesium and potassium levels.

- **Progress.** This lady settled after the repeat DC cardioversion but as she is at risk of sudden death she was referred to the cardiologist for further management. She was given an implantable cardioverter defibrillator.

ATRIAL FIBRILLATION

Prevalence and risks

Atrial fibrillation (AF) remains one of the most common and challenging of arrhythmias. It is estimated that 10% of the population will suffer from AF at some stage of their lives. Patients who remain in AF after their hospital admission face a long-term risk of embolism and stroke. This is reduced by the use of anti-coagulation, but long-term anti-coagulation also carries a risk. In an ideal world, all patients would be cardioverted to sinus rhythm but this might not be possible when there is underlying heart disease.

Case history (1)

A 76-year-old woman with a history of hypertension presents with a 6-week history of worsening palpitations accompanied by breathlessness.

On examination she is breathless getting undressed, she has a raised JVP, bibasal crackles, BP is 116/70 and her heart rate is 160. The ECG is compatible with **atrial fibrillation (AF)**.

Management

This woman has AF in association with heart failure. The CXR shows evidence of pulmonary oedema. You need to treat the heart failure (e.g. diuretics, ACE inhibitors) and control her ventricular rate with digoxin. Remember that a tachycardia might be an indication of poorly controlled failure or the AF might have tipped her into heart failure. Occasionally, poor LV function is secondary to poor rate control but more commonly poor rate control is secondary to poor control of CCF. In such cases where digoxin fails to control the rate (as in this patient), use amiodarone, which will improve rate control and the chance of cardioversion.

- **Progress.** She was anti-coagulated and proceeded to cardioversion as an outpatient. She converted to sinus rhythm but had to continue anti-coagulation for a further 3 months.

Remember

AF alone, without evidence of heart failure, can cause breathlessness.

Case history (2)

A 70-year-old woman with a history of hypertension presented to the hospital with a history of 6 h of palpitations. She had been taking 75 mg of aspirin prescribed by her GP for 2 years. The ECG showed atrial fibrillation at a rate of 132 beats per minute. The patient looked well and had a BP of 142/78 and there was no cardiomegaly on X-ray. She was clear that the symptoms started acutely 6 h previously so anticoagulation was not required.

Management

This patient reverted to sinus rhythm in response to a single DC shock (200 J). She remained in sinus rhythm at follow-up 6 months later.

The choices facing clinicians with a patient in AF are:

Should I cardiovert?

Yes, generally DC cardioversion is always worth trying at least once, provided there are no contraindications. Cardioversion can also be achieved with drugs but do not forget there is nearly as much of a risk of a thromboembolic event as with DC cardioversion, so these patients should be appropriately anti-coagulated. Amiodarone (200 mg \times 3 daily for 1 week then 200 mg maintenance per day) and class 1c drugs (e.g. flecainide) both promote cardioversion. [Figure 10.4](#) shows the sites of action of drugs on the heart but do not use flecainide in the presence of ventricular disease.

DC conversion (using a biphasic defibrillator) reverts AF to sinus rhythm in 80% of patients. This is the best treatment for AF of less than 24 h duration (see Case history 2, above).

What precautions should I take to prevent embolism at the time of cardioversion?

The risk of cerebral embolism can be markedly reduced by anticoagulation and patients who have been in AF for more than 24 h should be adequately anti-coagulated (INR $>$ 2) for a minimum of 3 weeks before and 4 weeks after elective cardioversion.

With a trans-oesophageal echo (TOE)-guided approach, patients do not need formal anti-coagulation prior to the cardioversion but should be covered with a full therapeutic dose of SC heparin before and during the procedure. If this is successful, they need another 4 weeks formal anti-coagulation with warfarin (or dabagatrim) post-procedure.

Remember, a patient suffering a stroke because of lack of anticoagulation in AF is negligent. A common misconception is that aspirin is as effective as warfarin, but this is not true. You need to make a careful risk-benefit analysis of the use of warfarin in elderly patients but in most of them the benefits will outweigh the risks.

Chads 2 score

How to assess the risk of thromboembolism in atrial fibrillation

Congestive heart failure	} all score 1 point
Hypertension	
Age $>$ 75 years	
Diabetes mellitus	
Stroke (including TIA)	scores 2 points
Total score	Stroke risk / y (%)
0: No anticoagulation	1.9
1: warfarin or aspirin	2.8
2 or greater: warfarin or apixaban	4.0
3	5.9
4	8.5
5	12.5
6	18.2

What should be done to promote good rate control in the long term if cardioversion fails?

Digoxin alone is often not effective in rate control and a second drug often needs to be added – beta blockers and verapamil are usually effective. There is no good evidence that digoxin promotes conversion to sinus rhythm and it should not be used in paroxysmal atrial fibrillation. The only good way to assess rate control is with a 24-h tape.

If this strategy fails, amiodarone is an excellent second-line treatment: it helps with rate control, makes cardioversion more likely and can be used with poor LV function, but remember that it does have long-term side effects. However, it can sometimes be effectively used at a lower dose (100 mg daily), with a lower risk of side effects, especially in the elderly.

Should I give prophylactic medication to prevent AF if sinus rhythm is achieved?

This depends on numerous clinical factors; the best drug is sotalol. You should discuss this with the cardiologist.

Which patients should I refer to an electrophysiologist (EP)?

Patients without evidence of underlying heart disease and who have either failed drug therapy or do not want to take any medication (usually young patients) should be referred for EP studies with a view to a definitive EP procedure to prevent further AF. However, any patient might potentially benefit from this approach, so if in doubt discuss any case with your cardiologist.

Remember

AF becomes more stable over time, and might be less easy to cardiovert the longer you wait.

Further reading

Camm AJ et al. Guidelines for management of atrial fibrillation. *Europace* 2010; **12**: 1–1360 European Society of Cardiology.

BRADYCARDIA AND PACING

Bradycardia due to increased vagal tone is a common finding in health and is also seen in an extreme form in vasovagal attacks when periods of asystole can occur.

Bradycardia is an increasing problem in the elderly and very elderly, and can reflect degenerative disease of the conducting system at all levels:

- Sinus node: sick sinus syndrome
- AV node: complete heart block, slow atrial fibrillation
- His–Purkinje system: bifascicular block (left axis deviation and right bundle branch block; RBBB).

Case history (1)

A 78-year-old man without any prior cardiac disease was brought to hospital after collapsing at home with brief loss of consciousness. On arrival he had fully recovered and the ECG showed bifascicular block. During monitoring overnight he was shown to have periods of **complete heart block**. He subsequently had a dual-chamber pacemaker (DDD) implanted without any recurrence.

Diagnosis

- Difficulties often arise in establishing arrhythmia as a cause of dizzy spells when the condition is intermittent, as it often is in the early stages.
- 24-h ECG is the best investigation but repeat tapes might be needed to demonstrate an abnormality when the history is very suggestive. Occasionally, in a patient with persistent symptoms and no findings on repeat ambulatory ECG monitoring, an implantable ECG recording device can help.

Classification of generic pacemaker code

Notation is by the following abbreviations:

- Chamber paced (0 = none, A = atrial, V = ventricular, D = both or dual).
- Chamber sensed (0 = none, A = atrial, V = ventricular, D = both or dual).
- Response to sensing (0 = none, I = inhibited, T = triggered, D = both T + I).
- Rate response (0 = none, R = rate modulation).
- Anti-tachycardia function (0 = none, P = anti-tachycardia pacing, S = shock, D = pace and shock).

For example: VVI = ventricular pacing, ventricular sensing, inhibition of pacing when beat is sensed; DDD(R) = dual pacing, dual sensing, inhibition and triggered as appropriate when beat is sensed, rate response mode available.

Pacemakers in common use

- VVI: usually for AF with slow ventricular rate and/or pauses.
- DDD: for complete heart block.

Rate response (R) is used when a patient has lost the chronotropic response, i.e. cannot increase the heart rate with exercise/stress. The cardiologist inserting the pacemaker will decide this but will need to know the patient's usual level of activity/independence to make this decision. AAI pacemakers are not often used in practice because a small proportion of these patients go on to develop coexisting AV nodal disease, so in anticipation of this dual-chamber pacemakers are usually implanted.

Pacemaker problems

All problems with pacemakers need to be referred to the pacing clinic; they will check the pacemaker and adjust its function as necessary. They will also refer to a cardiologist when necessary.

Surgical problems

- Infection is potentially very serious. Even slight redness around the scar should be treated promptly with antibiotics, e.g. flucloxacillin 500 mg \times 3 daily; if relevant, send swabs first. Usually occurs early after implantation.
- Haematoma can predispose to infection or technical problems.

Technical problems

- Fibrosis occurring around the pacemaker tip: this can cause pacemaker thresholds to rise, which can affect pacemaker function.
- Lead displacement: this will cause pacemaker malfunction, usually manifesting as failure to capture. It is most common in the first 6 weeks after implantation.
- Lead or pacemaker erosion through the skin: usually occurs long term.
- Pacemaker syndrome: vague feelings of weakness or dizziness in patients with VVI pacemakers and complete heart block. This is caused by loss of synchrony between atrial and ventricular contraction leading to episodic falls in BP and retrograde conduction of pacing impulse from ventricle to atria leading to simultaneous atrial and ventricular contraction. It is not seen with dual-chamber pacing and is treated by upgrading to a dual-chamber system.

Remember

If you suspect a pacemaker problem, always send the patient to a pacing clinic – that day – to have the function checked. The clinic will consult with a cardiologist if necessary. Out-of-hours, call the cardiologist on call.

Case history (2)

A 78-year-old man is admitted for a routine hip replacement. You are fast bleeped to the Orthopaedic ward; when you arrive the orthopaedic SHO tells you the patient is in 'VT'. You rush to see the patient, who is sitting up reading his newspaper. His rhythm strip from his preoperative ECG is shown (Fig. 10.5). What do you tell the SHO and what do you do?

- This is a paced rhythm but there is evidence of failure to capture.
- You ask the pacing clinic to check his pacemaker; they find that the sensing threshold has risen but all other parameters are fine. They increase his pacemaker output and his pacemaker function returns to normal.

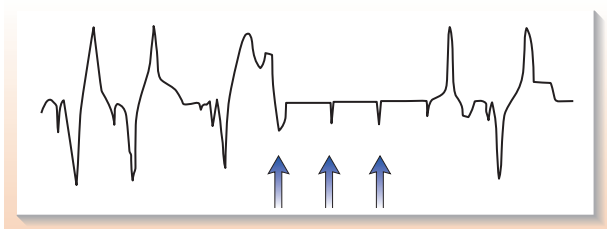


Figure 10.5 ECG showing pacing spikes (arrows) with failure to capture.

Remember

- Bradycardia and even transient conduction disturbance (first-degree and Mobitz type I or Wenckebach) can occur in healthy people during sleep. Great caution is needed when interpreting rhythm disturbances at night.
- Always take dizzy spells in a patient with a pacemaker seriously. Formal evaluation and an urgent pacing clinic check are required.

CARDIAC ARREST AND BASIC LIFE SUPPORT

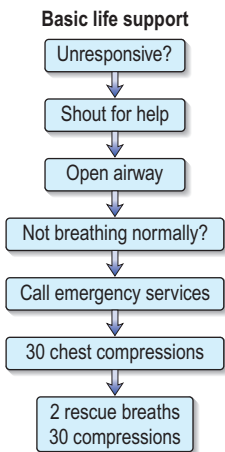
Case history

You are walking alone along an isolated corridor of your hospital. Just ahead, you observe a man collapse to the ground. As you approach you notice he is one of the hospital porters. He is lying motionless.

What should you do?

An assessment and initial resuscitation of the critically ill patient should be undertaken (ABCDE):

- **Airway** – remove any obstructing material and make sure airway is clear.
 - **Breathing** – look, listen and feel for signs of breathing.
 - **Circulation** – check carotid and peripheral pulses and start external chest compression if cardiac arrest.
 - **Disability** – conscious level – Glasgow Coma Scale (see [Table 15.3](#), p. 492).
 - **Examination/exposure**. – to allow a full examination to be carried out.
- Recent evidence emphasises that maintaining the circulation is the key factor overall.



Send or go for help as soon as possible according to guidelines

Figure 10.6 Basic life support. With permission from the Resuscitation Council.

The order of resuscitation should be CAB, i.e. Circulation, Airways, Breathing.

- Check for danger then shake and shout to check responsiveness.
- If there is no response shout for help.
- If no one responds to your call open the airway (Fig. 10.6).

What two methods could you use to open the airway?

1. Head tilt, chin lift.
2. A jaw thrust in suspected cervical spine injury.

There are no signs of breathing, you remain alone.

What must you do now?

You must leave the patient and go to the nearest telephone to initiate the cardiac arrest call.

You have initiated the emergency call from a telephone further along the corridor.

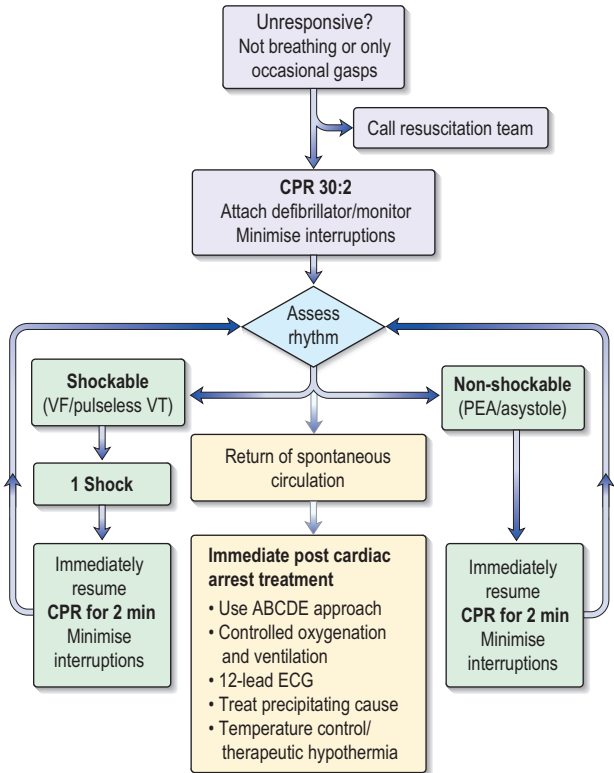
What should be your next action?

There are no signs of circulation after your assessment. The patient is cyanosed and motionless.

Commence basic life support (see Fig. 10.6).

Chest compressions – carefully note the following:

- Hand position: place the heel of the hand on the sternum, two fingers' breadth above where the rib margins meet.
- Arm position: lock the elbows and lean directly over the patient.
- Rate: aim to maintain a rate of 100 per minute.
- Depth: compress the chest one-third of the resting diameter of the chest.

**During CPR**

- Ensure high quality CPR: rate, depth, recoil
- Plan actions before interrupting CPR
- Give oxygen
- Consider advanced airway and capnography
- Continuous chest compressions when advanced airway in place
- Vascular access (intravenous, intraosseous)
- Give adrenaline every 3-5 min
- Correct reversible causes

Reversible causes

- Hypoxia
- Hypovolaemia
- Hypo/hyperkalaemia/metabolic
- Hypothermia
- Thrombosis - coronary or pulmonary
- Tamponade - cardiac
- Toxins
- Tension pneumothorax

Figure 10.7 Universal advanced life-support algorithm.

Table 10.3 AICDs – who needs referring for consideration of implantation of one?

Indications for implantation of AICD	
Primary prevention	Coronary disease, LV dysfunction (EF \leq 35%) and inducible VT
	High risk, inherited or acquired conditions, e.g. long QT syndrome, hypertrophic cardiomyopathy, Brugada's syndrome
	Chronic coronary disease, a history of MI and LV ejection fraction \leq 30%: from MADIT II*
Secondary prevention	Cardiac arrest due to VT/VF Sustained VT with structural heart disease
	Unexplained syncope with inducible sustained VT or VF with advanced structural heart disease and no other identifiable cause
AICD plus biventricular pacing	Any of above with QRS \geq 130 ms, LV dilation, LVEF \leq 30% and advanced heart failure

*Although this indication is backed up by evidence from the MADIT II trial, the healthcare cost implications are enormous and this is neither a routine indication in the UK at present nor likely to be in the near future.

- CPR at a ratio of 30 : 2 (30 compressions to 2 breaths), irrespective of number of rescuers.
- Continue this until the defibrillator arrives (Fig. 10.7).
 - **Progress.** The patient showed VF on the defibrillator and was successfully brought back into sinus rhythm with DC cardioversion. He was admitted and referred to the cardiologists.

He will need investigations to rule out structural heart disease (echo and angiogram). He will then need electrophysiological studies and an automatic implantable cardioverter defibrillator (AICD; Table 10.3) implanted to prevent recurrence because he has, in effect, had an 'out of hospital' VF arrest.

Information

- The chance of survival from ventricular fibrillation is generally agreed to deteriorate by 5–10% per minute. It is therefore imperative that a defibrillator is brought as soon as possible
- Alerting the team is a priority
- Give a praecordial thump if appropriate

CHEST PAIN (p. 336) AND ACUTE CORONARY SYNDROMES

Case history (1)

You are called to assess a 73-year-old woman who gives a 40-min history of sudden-onset, tearing, severe central chest pain radiating down her left arm and through to her back. She has a history of treated hypertension and has not smoked for 15 years. How are you going to manage her?

Initial assessment

Immediately, when she arrives:

- Brief history
- Risk factor profile (smoking, hypertension, lipids, diabetes, family history, age, gender, ethnic origin)
- Brief examination (BP, pulse, murmurs, chest signs)
- 12-lead ECG
- Give aspirin 300 mg orally
- Relieve pain, e.g. if ischaemic ECG give diamorphine 5–10 mg IV and an anti-emetic
- Take blood for markers of cardiac damage (troponins).

Remember

Every year patients are inappropriately discharged from A&E departments with acute coronary syndromes because their initial ECG is normal. If in doubt, admit the patient.

Causes of chest pain to consider

- Aortic dissection (see later)
- Acute coronary syndrome
- Pericarditis: sharp central pain, related to posture and respiration
- Pleurisy: sharp, usually lateral, related to respiration
- Muscular: related to posture, localised tenderness
- Herpes zoster: nerve root distribution, rash might appear later
- Gastro-oesophageal reflux disease: retrosternal burning pain but can be very similar to angina.

Note: Many episodes of chest pain do not easily fit into any category and patients are often admitted and treated for acute coronary syndromes. Their symptoms should be assessed in conjunction with their risk factor profile. If in doubt, it is safer to admit.

What features would make you suspect a dissecting aneurysm?

- Pain tends to radiate to back, starts abruptly and is often intense and described as tearing.

- On examination: absent arm or leg pulses, murmur of aortic regurgitation, different BP in arms, neurological signs.
- ECG might be normal or show inferior ischaemia or MI.
- As the dissection in the aortic wall extends proximally, first it disrupts the origin of the subclavian arteries (affecting arm BP), then the carotid arteries (causing neurological sequelae), the origin of the right coronary artery – causing inferior ischaemia – and finally the aortic valve is disrupted causing aortic regurgitation.

If you clinically suspect a dissecting aneurysm you must

- Get a chest X-ray to look for mediastinal widening.
- Get a senior opinion.
- *Never* give thrombolytic therapy, heparin or anti-platelet therapy.
- Carefully reduce BP with IV labetalol or sodium nitroprusside.
- Discuss with a cardiothoracic centre.
- CT with contrast or an MRI with contrast: although trans-oesophageal echo (TOE) is an excellent investigation it must be done by a very senior operator and should really be done in the cardiothoracic centre with surgeons on standby.

Case history (continued)

The patient's ECG now changes at approximately 20 min with 4 mm of convex up-sloping ST elevation in leads II, III and AVF. The diagnosis is, of course, an **inferior ST elevation MI (STEMI)**.

Immediate medical management in A&E

All hospitals are expected to have a rapid triage for chest pain to ensure that all suspected ACS patients are seen without delay. There should be a multi-disciplinary team approach with defined guidelines. With all ACS patients:

- IV access should be gained and bloods sent for cardiac markers, biochemistry, lipid profile, FBC and clotting profile.
- **Oxygen** is no longer recommended in the 2008 British Thoracic Society guidelines, unless the patient is hypoxaemic (check on pulse oximeter).
- **Aspirin** 300 mg chewed, then 75–150 mg daily, should be given.
- **Sublingual glyceryl trinitrate (GTN)** 0.3–1 mg should be given for pain relief, repeated as necessary (provided BP is not compromised). This can be followed by an IV infusion of 1–10 mg/hour, which is titrated to pain whilst aiming to keep systolic BP > 100 mmHg.
- **IV diamorphine** 2.5–5 mg or **morphine** 10 mg is used as analgesia, with metoclopramide 10 mg as an antiemetic.
- IV β -blockade with **metoprolol** is given in 5 mg boluses (up to a total of 15 mg), provided the patient is not in cardiogenic shock and/or hypotensive, and that there are no contraindications (e.g. asthma).
- Patients with a STEMI ideally should start β -blockers on the first day, provided they are definitely haemodynamically stable. If there is any doubt, wait until they are stable, to avoid the possibility of cardiac shock developing.

- All ACS patients should be transferred to a coronary care unit (CCU) for continuous monitoring and further specialist care.
- Patients with ACS should have **clopidogrel** 600 mg loading dose, unless PCI is not being done, in which case the loading dose should be 300 mg; thereafter 75 mg daily is given in addition to aspirin. It has been shown to reduce mortality and the occurrence of major vascular events without an increase in the risk of bleeding in STEMI ACS. Prasugrel 60 mg is an alternative
- **N.B.** Proton pump inhibitors, particularly omeprazole, reduce the antiplatelet effect of clopidogrel because they are inhibitors of cytochrome p450 (CYP2C19), but have only a small therapeutic effect.
- In addition, urgent reperfusion (see below) is needed.

THROMBOLYSIS

Thrombolysis is still used in some hospitals.

You must know the indications for thrombolysis:

- A history of typical ischaemic chest pain, which started within the last 12 h.
- A 12-lead ECG that shows at least one of:
 - 1 mm or more of ST elevation in two or more limb leads *or*
 - 2 mm or more of ST elevation in two or more adjacent precordial leads *or*
 - New-onset left bundle branch block.
 - **Progress.** This patient fulfils the criteria for PCI but this is not available. She should have thrombolysis, unless there is a contraindication (Table 10.4).

Thrombolytic therapy

Alteplase ('accelerated' recombinant tissue-type plasminogen activator; rtPA) 1 mg/kg over 60 min (remember you must give concomitant IV heparin or LMWH for the first 24 h with rtPA).

Table 10.4 Contraindications to giving thrombolytic therapy

Absolute contraindications

Aortic dissection
 Surgery or procedure within last month
 Stroke within the last 6 months or coma
 Recent GI haemorrhage or symptoms suggesting active peptic ulcer
 Severe liver disease, oesophageal varices or acute pancreatitis
 Trauma with risk of haemorrhage
 Haemorrhagic diathesis
 Systolic BP > 200 mmHg

Relative contraindications

Pregnancy or active menstruation
 Proliferative diabetic retinopathy
 Known aortic aneurysm or intracardiac thrombus
 Known anticoagulant therapy

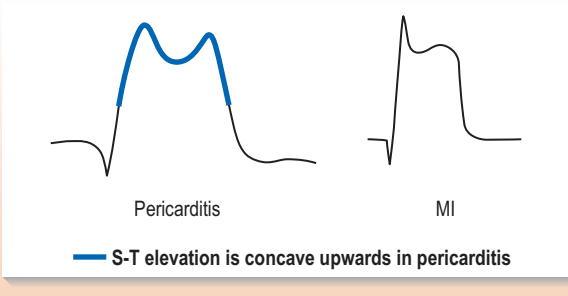


Figure 10.8 ECG changes in pericarditis and myocardial infarction.

Remember the other thrombolysis drugs that are available. For example, some hospitals use tenecteplase, which is an easy-to-administer single bolus thrombolysis agent of proven benefit in large trials. If a patient has any type of contraindication to thrombolysis you must discuss the case with a cardiologist immediately.

Don't forget pericarditis!

ST changes in pericarditis are often widespread, involving inferior as well as anterior leads (Fig. 10.8) but the ST changes are concave with peaked T waves and there is often associated widespread PR depression (a feature specific to pericarditis).

Also beware

- LBBB: if this is known to be old, the diagnosis will rest on the history and cardiac enzymes; it can be difficult to distinguish acute changes on a background of LBBB. If it is known to be new it can be used to support the diagnosis.
- Other (non-ischaemic) causes of ST elevation:
 - High S-T take-off is seen more commonly in certain racial groups, e.g. Afro-Caribbean
 - There are other causes you should be aware of such as the ST elevation seen in leads V1–3 in patients with Brugada's syndrome.

Cardiac markers in the early assessment of a patient with chest pain (Fig. 10.9)

Troponins start to be released within minutes of myocardial damage and are very useful. But, apart from the patient with known LBBB, they rarely play a role in the initial management decisions at the time of admission in patients with acute coronary syndromes. They should, however, be measured both at admission and at 24 h in all patients with a suspected acute coronary syndrome. Most other cardiac markers take several hours to rise, might be misleading and are now used much less, given the availability of troponin assays.

- **Progress.** This 73 year old lady with a STEMI was given thrombolysis with alteplase. She was seen by the coronary rehabilitation team.

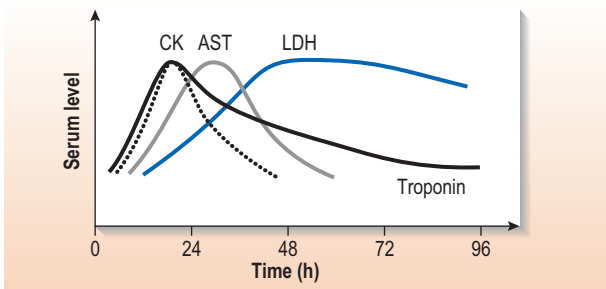


Figure 10.9 Enzyme and troponin profile in acute myocardial infarction.

Table 10.5 Definition of myocardial infarction (MI)

Both the following definitions satisfy the diagnosis of an acute, evolving or recent MI.

1. Typical rise and gradual fall of troponin with at least one of the following:
 - Ischaemic symptoms (chest pain)
 - ECG changes indicative of ischaemia (e.g. ST depression or elevation, T wave changes)
 - Development of pathological Q waves on the ECG
 - Following coronary artery intervention, e.g. angioplasty
2. Pathological findings of an acute MI (usually dead patient)

The classification of acute coronary syndromes

The term 'acute coronary syndrome' covers the spectrum from unstable angina to MI. This has been a rapidly evolving area (Table 10.5). With this in mind, the decisions to make, using this definition, are:

1. Is this an ST elevation MI (STEMI) or a non-ST elevation MI (NSTEMI)?
2. Or is this unstable angina?

This helps you direct your therapy; patients with an STEMI should receive PCI or thrombolysis. It is easy to appreciate from the pathogenesis (Fig. 10.10) how failure to treat unstable angina can allow progression to an MI. All the patients should initially be admitted to CCU for management.

Symptoms suggestive of an acute coronary syndrome

- Angina occurring at rest, at night or on minimal effort.
- The pain might require escalating doses of GTN.
- It might be associated with sweating, nausea or breathlessness, especially in an MI.
- There might be a background of worsening exertional symptoms prior to the admission episode of pain.

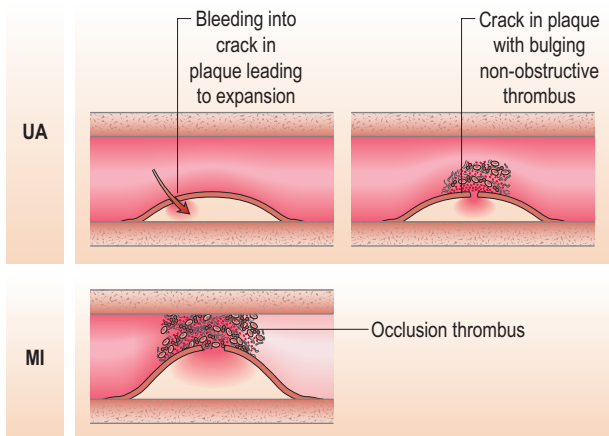


Figure 10.10 The pathology of unstable angina (UA) versus acute myocardial infarction (MI).

Case history (2)

You are about to finish your shift when a casualty officer asks you 'while you are here' to look at the ECG of a patient who is about to be sent home. The patient is a 44-year-old male smoker who has had anterior central chest pain on and off at rest for the past 2 days. The first ECG shows some subtle T wave changes in the anterior leads but his repeat ECG is normal and he is now pain free, having had the GTN. The casualty officer has told him he can go home with a GTN spray and come back to clinic in 6 weeks. The patient is pleased and is sitting, fully dressed, waiting for his GTN spray, because he is keen to get home to watch the football. Can he go home?

What do you say and do?

- This patient absolutely cannot go home! He needs admission, treatment for **unstable angina and risk stratification**. This is exactly the type of patient who, if sent home, will go on to have an MI. Admit him to CCU.

Remember

Management of MI depends on a fast-track approach: 'time is muscle'.

- Therapy:
 - *Aspirin* 300 mg loading dose then 75 mg daily thereafter; in addition to this give him 300 mg loading dose of *clopidogrel* and 75 mg daily thereafter (CURE trial).

Continued

Remember (continued)

- Start the patient on SC *low molecular weight heparin* (LMWH), usually Enoxaparin (1 mg/kg × 2 daily).
- Start him on a *beta blocker*, such as metoprolol 25 mg × 3 daily (unless contraindicated); patients with a sinus tachycardia or hypertension will benefit most from this and should be given early IV beta blockade.
- Put him on an IV *GTN infusion* (0–10 mL/h, titrate according to pain and BP).
- Assess and correct *risk factors* (smoking, lipids, hypertension, diabetes).
- Ensure a *troponin* is sent at the time of admission and the following day.

Remember

- If the initial ECG is normal: do not discharge the patient. It is possible to have a normal ECG in an acute coronary syndrome
- Repeat the ECG every 20 min for at least 1 h
- Consider other causes of chest pain.

His further management will depend on risk stratification using his troponin (at 24 h), symptoms and ECG. If his symptoms settle:

- If he is troponin positive (high risk) he should be referred for immediate inpatient PCI.
- If he is troponin negative, low risk requiring further investigation, e.g. coronary artery imaging, he can be managed medically initially but will need discussion with the cardiology department.

Remember

There are many other causes of a raised troponin, e.g. pericarditis, pulmonary embolism, myocarditis.

If his symptoms do not settle:

- He will need urgent inpatient angiography; in the meantime his medical therapy should be increased.
- If he is troponin positive and has dynamic ECG changes he should be started on an IV glycoprotein IIb/IIIa antagonist infusion and referred for angiography that day.

Note: IIb/IIIa antagonist infusions have not been proven to be of benefit as medical therapy alone. A GP IIb/IIIa antagonist, e.g. abciximab, should be given before PCI and for 12 hours post PCI. If a patient does not go straight away for a PCI, he should receive an infusion of either tirafibam

or eptifibatide. The dosing is complex and you need to look it up (e.g. in a *National Formulary*).

A brief note on glucose and statins

Any patient with an abnormal admission glucose should be started on an IV insulin sliding scale (see p. 424); there is evidence that this improves outcome. High-dose statins (e.g. atorvastatin 80 mg daily) should be started on admission because there is evidence that they improve prognosis above and beyond their lipid-lowering effects, by stabilising the acute plaque.

Remember

- Do not miss an aortic dissection! Giving such a patient thrombolysis is dangerous and likely to be fatal
 - If in doubt about whether to give thrombolysis discuss the patient with a cardiologist immediately; if thrombolysis is contraindicated coronary intervention may well be a viable option.
- **Progress.** In this patient the troponins were normal. As his symptoms had settled he was sent home with medication for an angiogram as an outpatient.

Case history (3)

A 62-year-old man with type 2 diabetes was admitted to hospital with a 6-h history of central chest pain radiating to both shoulders and to his jaw. The ECG in A&E showed 2 mm of ST segment depression in the inferior leads. His troponin T was elevated at 0.9. The diagnosis was a NSTEMI. The pain settled with medical therapy and he was referred for PCI.

His angiogram showed a single tight mid-right coronary artery stenosis but no other significant disease. He went on to have a successful angioplasty and a stent, with excellent results.

ACUTE MYOCARDIAL ISCHAEMIA – WHO NEEDS ACUTE INTERVENTION?

This is a very rapidly evolving field because of constant advances in techniques and biomechanical engineering, i.e. stent technology. As a result, there is a lot of clear evidence from numerous large trials showing improved outcome with percutaneous intervention in certain groups of patients (FRISC II, Tactics-TIMI 18, GUSTO IV ACS, RITA III – to name just a few). Broadly speaking, these can be put into one of three groups:

1. *ST elevation MI (STEMI)*:
 - i Primary intervention: there is now clear evidence that percutaneous coronary intervention (PCI) is better than thrombolysis for acute

STEMI. There is no doubt that, given appropriate resources, infrastructure and staff, this is the treatment of choice. In the UK thrombolysis is still used although PCI is becoming more readily available.

- ii Secondary intervention: patients who are reinfarcting, in whom thrombolysis has failed to resolve the ECG findings and symptoms, have post-infarct angina or have VT after the first 24 h should be discussed urgently with a cardiologist with a view to urgent PCI.
2. *Non-ST elevation MI (NSTEMI)*: these patients should be referred for immediate PCI. If PCI is not available, give fondaparinux 2.5 mg sc daily with aspirin 75 mg as they represent a high-risk group for further subsequent events.
3. *Unstable angina*: patients with ongoing symptoms despite medical treatment with evidence of ischaemia should be discussed with a cardiologist for consideration of PCI.

In the long term, the value of revascularisation – whether by surgery or PCI – in relieving persistent symptoms is beyond doubt. Revascularisation should be considered in all outpatients taking into account their symptoms, lifestyle and investigation results. Generally, bypass surgery is used in: left main stem disease, three-vessel disease, diffuse disease with a poor ventricle and diabetics.

CARDIOGENIC SHOCK

Information

Definition: persistent hypotension (< 90 mmHg systolic) associated with reduced end organ perfusion due to low cardiac output.

This is usually the result of acute myocardial infarction and is manifested by poor peripheral perfusion and low urine output, often associated with clinical/radiological evidence of LVF. Mortality approaches 80% with treatment and is much higher without. Predisposing factors include:

- Old age
- Previous MI
- Large anterior MI
- Prior hypertension/diabetes
- Inadequate or late thrombolysis.

Case history

You are called at 2 a.m. to see a 68-year-old diabetic woman who was admitted with a 12-h history of chest pain and ECG changes of an extensive anterior MI. She was treated with alteplase at 2 p.m. the previous day. She has previously had an inferior myocardial infarct. She has remained hypotensive with a poor urine output since admission and is now feeling very unwell. Her current CXR is clear. What do you do?

Management (Fig 10.11)

- Get a repeat ECG to look for evidence of reperfusion or continuing ischaemia.
- Check that patient is not volume depleted; this must be done using at least a CVP line and preferably a Swan–Ganz catheter on CCU.
- Check that there is no structural cause: get an urgent transthoracic echo:
 - Ventricular septal rupture (murmurs at left sternal edge – may be inaudible if large) usually occurs after 2–3 days
 - Papillary muscle rupture giving severe mitral regurgitation (usually murmur but might be silent).

Remember

An urgent echocardiogram should be performed in every patient with cardiogenic shock.

- Give inotropes intravenously if there is no response to volume replacement:
 - Dobutamine and/or low dose dopamine
 - If possible, try and avoid adrenaline (epinephrine) or noradrenaline (norepinephrine) because they will worsen any ischaemia.
- Discuss with cardiologists immediately with a view to transfer for PCI:
 - This is particularly appropriate in the patient with an anterior MI and no previous history of IHD where cardiac stunning might be present.
 - In the SHOCK trial, patients referred for early intervention (within 24 h of onset) had an improved prognosis – time counts.
- Insert an intra-aortic balloon pump (IABP), if available: this is a highly effective way of improving cardiac perfusion, and should be used in any patient in whom there is a reasonable prospect of further definitive treatment (e.g. revascularisation/repair VSD). Cannot be used in the presence of significant aortic regurgitation.
 - **Progress.** This patient was treated with intravenous dobutamine with some initial improvement in BP and peripheral perfusion, but 24 h later she remained anuric and developed acute pulmonary oedema and shock unresponsive to increasing inotropic support. By the time she was discussed with the cardiologists she had been anuric and shocked – with a systolic BP of 65 despite inotropes – for 36 h. She was too unstable to transfer and she died shortly after.

Remember

Do not go to bed when you have a patient in cardiogenic shock (who is appropriate for aggressive treatment). Stay up, get on the phone to the cardiologists quickly and sort it out. It is hopeless referring a patient 36 h later: by this time he or she will not be treatable.

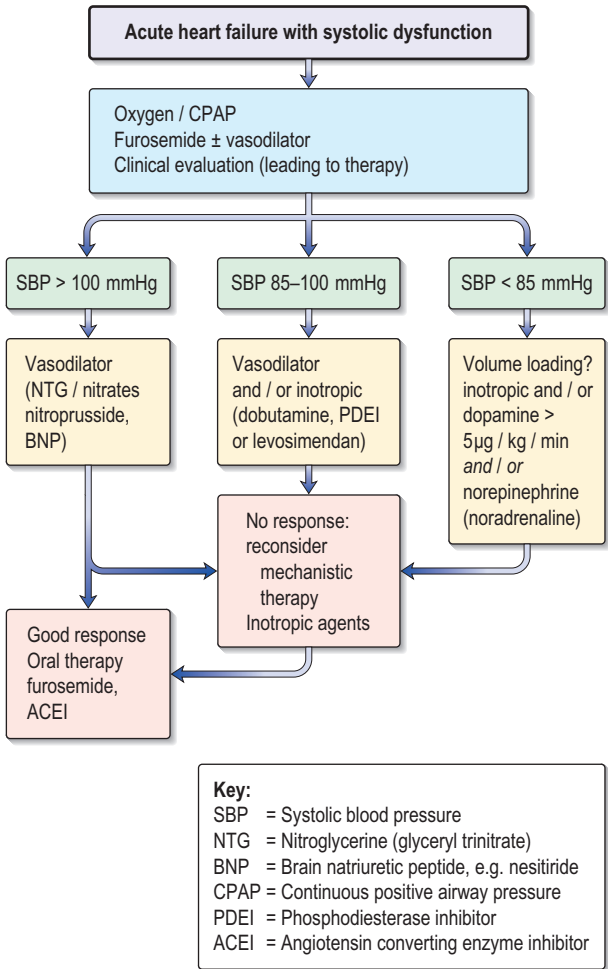


Figure 10.11 Algorithm for the management of acute heart failure with systolic dysfunction. From Nieminen MS, Böhm M, Cowie MR et al. *European Heart Journal* 2005; 26: 364–416, Fig. 6, with permission from Oxford University Press and the European Society of Cardiology.

Remember

- There is **never** a role for renal dose dopamine in any patient with renal failure
- In patients on prior beta blockers, competitive blockade may persist for 24 h or more and will require much higher doses of dobutamine/dopamine
- It is probably simpler in this situation to use milrinone/enoximone, which bypasses the beta adrenoceptor.

Information

Myocardial stunning and hibernating myocardium

- When heart muscle is subjected to acute ischaemia it might cease to contract but remain viable. This is a potentially reversible cause of haemodynamic problems in acute MI.
- **Myocardial stunning.** If the blood supply to the relevant area is restored as a result of natural recanalisation of occluded arteries, pharmacological thrombolysis or angioplasty, the functional capacity might return relatively quickly – over a matter of a few hours. Such myocardium is called stunned myocardium.
- **Hibernating myocardium.** A similar state of affairs might occur on a more chronic basis, usually in severe three-vessel disease. In this case, the cellular ultrastructure might become seriously deranged even though the ischaemic myocytes are still potentially viable. This is known as hibernating myocardium; such myocardium can be restored by revascularisation.

These major changes, which have occurred at the cellular level, mean that the period of recovery might be over weeks or even months. PET scanning, stress echocardiography and radionuclide myocardial perfusion scanning can all be used to identify hibernating myocardium.

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction is often associated with volume-dependent hypotension that responds well to fluid replacement.

Case history

A 58-year-old man is admitted with an inferior MI (Fig. 10.12) and is given successful thrombolysis within 2 h of the onset of pain. Although ST elevation and pain largely resolve within 1 h, he remains hypotensive with a systolic BP of 70–80 mmHg associated with a low urine output.

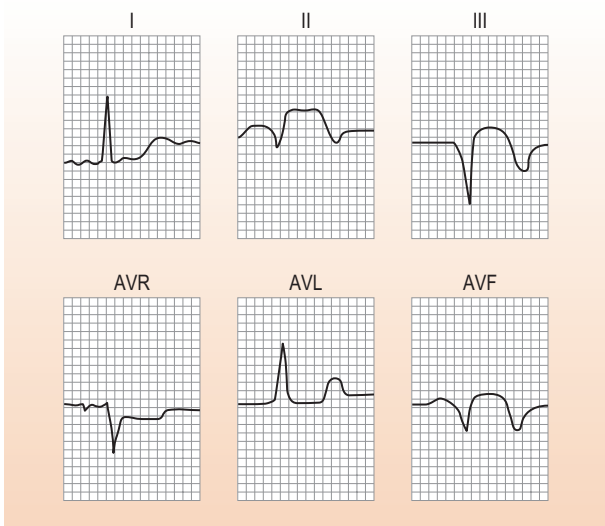


Figure 10.12 An acute inferior wall myocardial infarction. Note the raised ST segment and Q waves in the inferior leads (II, III and AVF).

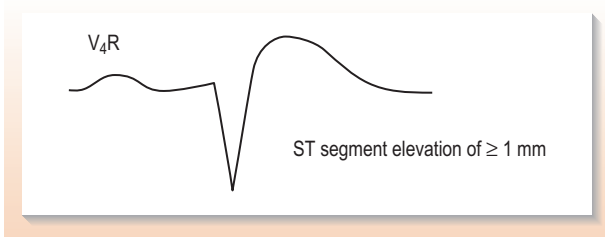


Figure 10.13 Right ventricular infarct.

Case history (continued)

A further ECG with right-sided chest electrodes (Fig. 10.13) suggests right ventricular infarction with ST elevation in V₃R–V₄R. A fluid challenge of one litre of 5% glucose, given over half an hour IV, restores the BP to 110 systolic with a good urine output.

Intravenous fluids in an acute MI should be given using an appropriate measure of the patient's filling status, such as CVP (via a central line) or using Swan-Ganz (pulmonary artery) catheter readings.

Right ventricular infarction is:

- Diagnosed readily by elevation of ST segment in V3R-V4R on right-sided ECG
- Associated with volume-dependent hypotension
- Often associated with elevation of JVP without other evidence of heart failure
- Associated with a higher incidence of all post-MI complications, e.g. arrhythmias, cardiac rupture.

Heart failure and cardiogenic shock usually reflect extensive cardiac damage but cardiac 'stunning' might be present, and active treatment can save lives.

- **Progress.** He was given medical therapy with aspirin, clopidogrel, β blockers and LMWH and was stable after 5 days. He was referred for urgent PCI.

HEART FAILURE FOLLOWING AN MI

Case history

A 63-year-old man has been on CCU for 5 days following his second myocardial infarction. He has been managed with percutaneous coronary intervention and on this occasion has had two eluting stents in his left anterior and circumflex arteries.

You are asked to see him because he has felt breathless over the last hour.

On examination he is tachypnoeic with a pulse of 90/min and a BP of 140/80. His venous pressure is raised and he has a gallop rhythm and basal crackles. You diagnose **acute heart failure**.

The presence of heart failure, even if transient or only evident on CXR or echo, places the patient with an MI in a far worse prognostic group.

Acute heart failure in the context of an acute MI is associated with a very high inpatient mortality.

Treatment

- IV diamorphine boluses 2.5–10 mg.
- An IV nitrate infusion (0–10 mL/h), titrated to blood pressure and symptoms.
- Boluses of IV furosemide 40–80 mg, although an infusion is better in severe heart failure.
- Invasive monitoring to help to guide therapy.
- IV inotropes if patient remains hypotensive despite the above measures.

Treatment of underlying poor ventricle

- Introduce ACE inhibitor (or angiotensin receptor antagonist) as soon as possible: ACE inhibitors have been shown to reduce the mortality of

this high-risk group by 20–30%. Initiate this therapy as soon as the patient is off inotropes, haemodynamically stable and has stable renal function. Ramipril (1.25 mg initially) is a good choice given its simple dosing regime. A slight deterioration in renal function (up to 30%) might be seen, and if this happens do not increase the dose. If, despite this, renal function continues to worsen, withdraw the ACE inhibitor and reconsider at a later date.

- The introduction of a beta blocker as soon as it is safe: there is a wealth of evidence supporting the use of beta blockers in heart failure to improve prognosis. Evidence from the CAPRICORN and COPERNICUS trials showed that even patients with severe heart failure benefit from the cautious introduction of beta blockers, (provided the patients are not on IV inotropes or vasodilators) e.g. carvedilol, starting at 3.125 mg × 2 daily or bisoprolol, starting at 2.5 mg daily).
- Spironolactone 12.5–25 mg daily (if the heart failure is moderate to severe).
- Consider further revascularisation: remember patients will benefit from revascularisation if part of their poor ventricular function is due to viable stunned or hibernating myocardium. All patients with post-infarct cardiac failure should be seen by a cardiologist.
 - **Progress.** The patient was treated intensely with diuretics, an ACE inhibitor and a β blocker. He made a very slow recovery but was able to be discharged in 2 weeks and followed up by the cardiologists.

POST-INFARCTION ARRHYTHMIAS AND HEART BLOCK

Case history (1)

A nurse on CCU calls you at 5 a.m. A 56-year-old man without previous heart disease was admitted with an inferior MI and had had successful thrombolysis at 11 p.m. the previous evening. The nurse had been looking at the monitor and noticed that the patient kept having ectopics and has had two short five-beat bursts of non-sustained VT. The nurse wants you to 'review' the patient. When you arrive the patient is lying flat, fast asleep with a heart rate of 50 (sinus rhythm) and haemodynamically stable. He was given a beta blocker on admission and when you look at his results all his electrolytes (including Mg^{2+} and Ca^{2+}) are normal. You reassure the nurse who, however, is 'just not happy' and wants you to prescribe something.

What do you do?

- Reassure the nurse that anti-arrhythmics are not indicated. In the CAST trial, post-MI patients with asymptomatic ventricular arrhythmias were randomised to anti-arrhythmic drugs or placebo; the patients given anti-arrhythmics had a worse outcome.
- There is no role for giving empirical IV Mg^{2+} to all patients with an acute MI, as shown by the MAGIC trial.

Arrhythmias – atrial and ventricular – are common in the first 24 h after an MI and might be life threatening. For this reason, all these patients must be in monitored beds on CCU. Late arrhythmias (after the first 24 h) are of more prognostic significance and will require specialist evaluation.

Early ventricular arrhythmias

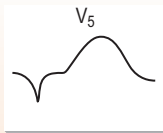
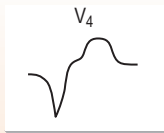
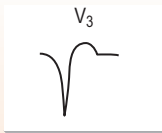
- Ectopics and non-sustained VT are very common, particularly in the 1–2 h after thrombolysis ('re-perfusion arrhythmias') and usually require no treatment. Check K^+ , Mg^{2+} and Ca^{2+} and correct if needed.
- Sustained VT or after VF: Standard practice is IV bolus 100 mg over 5 mins, then infusion of 2–4 mg/min) for 24 hrs after cardioversion. Amiodarone is also used.
- Early use of IV beta blockers, e.g. metoprolol, often reduces incidence of ventricular arrhythmias.
 - **Progress.** This patient's arrhythmias settled without the need for anti-arrhythmics. He was discharged with an outpatient appointment with the cardiologist.

Case history (2)

A 72-year-old woman with diabetes was admitted with an anterior MI and received thrombolysis 8 h after the onset of pain. The CXR showed pulmonary venous congestion. The ECG after thrombolysis is shown in [Figure 10.14](#).

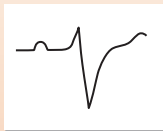
During the night, nurses observed isolated non-conducted P waves but no action was taken. The next morning the patient collapsed with a heart rate of 28/min and complete heart block; she had not passed urine since admission. A wire was passed via the internal jugular route and she was successfully paced. Despite this, she developed increasing heart failure and died 2 days later.

Before



Note: ST elevation and Q waves typical of acute MI

After



Bifascicular block – note prolonged PR interval and broad QRS complexes

Figure 10.14 ECG following thrombolysis in this patient.

Heart block

Management is usually very different for inferior and anterior MI. In inferior infarcts a conduction disturbance is common and, provided the patient is not haemodynamically compromised, temporary pacing is usually not required and the problem resolves within 2 weeks; permanent pacing is rarely required. However, heart block in anterior infarcts invariably represents extensive myocardial damage and nearly always needs pacing (temporary and permanent).

Information

Indications for temporary pacing post-MI

- Mobitz II heart block with anterior MI.
- Third-degree (complete) heart block (CHB) with inferior MI if hypotensive or cardiac failure, *always* with anterior MI.
- Bifascicular block (RBBB with left or right axis deviation): usually anterior MI and at risk of CHB.
- Trifascicular block (long PR interval and either LBBB or RBBB with axis deviation): usually anterior MI and at risk of CHB.
- Alternating LBBB and RBBB: usually extensive myocardial injury and high risk of CHB.

Note: Do not use the subclavian route after thrombolysis – instead use either the jugular or femoral route because there is less risk of haemorrhagic complications.

Management of late arrhythmias

- Atrial fibrillation/SVT: commonly associated with pericarditis or heart failure. Usually self-limiting or responds to digoxin. Consider cardioversion if this fails or the patient is compromised. Treat pericarditis or cardiac failure actively.
- Ventricular tachycardia: as a late event carries a bad prognosis.
- Beta blockers: all patients should be on these unless contraindicated.
- IV amiodarone: if recurrent VT that has not settled with beta blockers.
- All patients must be referred for early inpatient angiography and appropriate electrophysiological investigations and management as necessary (usually implantation of an internal defibrillator).
- Avoid other anti-arrhythmics, especially those that are negatively inotropic, e.g. flecainide.

Remember

Ventricular 'escape' rhythms are common in bradycardia due to increased vagal tone, and usually respond to atropine.

Information

Anterior MI and complete heart block carry a very high in-hospital and 1-year mortality.

MYOCARDIAL INFARCTION – SECONDARY PREVENTION

The greatest concern of patients who have recovered from a heart attack is whether they will have another. As well as lifestyle changes, there are a wide range of drugs available for secondary prevention, with strong evidence to support their use. The following should be undertaken:

- Stop smoking
- Strict control of blood pressure
- Diet modification with a view to appropriate weight loss: low fat, low salt, fish oils, high vegetable content
- Exercise
- Drug therapy.

Drug therapy

Antiplatelet therapy

Aspirin

- Dose: 75 mg daily.
- Contraindications: clear history of type 1 allergic reaction (angio-oedema, anaphylaxis), in which case give clopidogrel 75 mg daily. If there is a history suggestive of peptic ulceration disease, give a proton pump inhibitor. *Note:* later check for the presence of *Helicobacter pylori* and eradicate.

Clopidogrel

- Dose: 75 mg daily for 12 months after acute episode. Alternatively, Prasugrel 10 mg daily can be used.

Beta blockers

- Should be used in all patients.
- Evidence: 20–25% mortality reduction; greatest benefit in the high-risk group (prior MI, diabetes, transient heart failure). Probably a class effect but documentary evidence for: propranolol, timolol, metoprolol, acebutolol (not atenolol, although this is the most widely used drug in British practice).
- Contraindications: reversible airways disease.

Calcium channel blockers

- Non-dihydropyridines: should not be routinely used and in STEMI have not been shown to improve mortality (INTERCEPT trial). However, they can be given in patients in whom beta blockers are contraindicated when rate control is needed.
- Dihydropyridines, e.g. nifedipine: have no place in secondary prevention and might be harmful.

Angiotensin converting enzyme inhibitors (ACEI)

Should be given to all patients with post-acute coronary syndrome (HOPE trial); those with reduced ventricular function obtain most benefit. There are many large trials to show this. Although it is probably a class effect,

ramipril, lisinopril and tranolapril are most commonly used; captopril is less used because it causes the worst first-dose hypotension.

Monitor BP and renal function (see earlier). If ACEI are contraindicated or not tolerated due to cough, an angiotensin receptor antagonist such as losartan is given. In the VALIANT trial it was shown that valsartan is equivalent in efficacy to, but no better than, an ACE inhibitor.

Lipid-lowering drugs

'Statins' should be given to all patients because there is a huge amount of evidence backing their use in primary (WOSCOPS) and secondary prevention (4S trial) in ischaemic heart disease. This is highly likely to be a class effect. Pravastatin has the best side effect profile but atorvastatin is more powerful in reducing cholesterol. According to UK National Service Framework (NSF) guidelines, you should aim for a total cholesterol of less than 5, or a 25% reduction, whichever produces the best effect. These should be started on the day of admission (ensure a lipid profile has been sent; see earlier). Occasionally, myalgia/myositis can occur in the first few weeks in some patients. Do not forget to look at and treat low HDLs.

Anti-coagulation

There is no evidence that this is routinely of any benefit. However, it might be valuable in some patients:

- Those with proven LV thrombus, those at risk of LV thrombus (large ventricle and LV dysfunction)
- Those with AF.

Summary of drugs required for secondary prevention

- Aspirin for all
- Statins for all
- Beta blockers for all, unless contraindicated or not tolerated
- ACEI for all, unless contraindicated or not tolerated
- Calcium antagonists for selected patients, e.g. intolerance to beta blockers.
- Anti-coagulation for selected patients.

Identifying 'high-risk' survivors of MI

- Prior IHD, hypertension, diabetes mellitus
- Heart failure (even transient)
- Late arrhythmias (> 24 h after MI)
- Age > 60 years
- Impaired ventricular function
- Unable to perform exercise tolerance tests (ETT) because of cardiac symptoms.

Remember

- All patients should be offered cardiac rehabilitation
- Strict blood sugar control improves prognosis in diabetics; a 3-month regime of SC insulin is often needed
- After MI, the lipid levels might fall for up to 2 months. Ideally, check the lipid profile at this stage, although statin therapy is given (after a random cholesterol has been sent) at presentation
- High-risk patients benefit most!

HEART FAILURE RECOGNITION AND ACUTE MANAGEMENT

Differentiating heart failure from lung disease as a cause of breathlessness can be difficult because there is often coexisting cardiac and respiratory disease. In the case of smokers, this usually consists of ischaemic heart disease and COPD. There is thus a tendency to give a concoction of therapy to cover both cardiac failure and an exacerbation of COPD, often with antibiotics being added in to cover infection, especially in the elderly. This section will attempt to provide a diagnostic route to clarify the problem and seek therapeutic solutions.

Case history

At 3 a.m., an SHO in A&E refers you an 80-year-old man with a 4-day history of increasing breathlessness, wheeze and non-productive cough. He lives alone in a first-floor flat and smokes 10 cigarettes a day. The SHO is not sure what the diagnosis is but thinks it might be a 'chest infection'.

Is it heart failure?

Remember that wheeze and cough occur in heart failure as well as respiratory disease. Although the onset of breathlessness is often rapid in heart failure, it can also be rapid in respiratory disease. Clinical examination might help you further differentiate the two but you often need the results of investigations to help differentiate the causes.

- In heart failure the ECG will almost always be abnormal.
- The echo will invariably show depressed systolic function (but beware of a small percentage of patients with diastolic heart failure and normal systolic function).
- The CXR will help as will respiratory function tests (but remember respiratory function tests may be of no help in the acute phase).
- Serum natriuretic peptides are useful in the diagnosis of heart failure; serum BNP >200.
- Assess response to therapy.

Case history (continued)

The patient gives you a history of a sudden onset of breathlessness, preceded by dull chest pain, which started 4 days ago. On examination he is apyrexial, tachypnoeic and sitting up; he has crackles at both his lung bases, a small left-sided pleural effusion, a raised JVP and a BP of 160/95. His ECG showed an old anterior myocardial infarction.

He clearly has **left ventricular failure**, the aetiology of which is likely to be due to ischaemic heart disease with hypertension.

Common causes of acute cardiac failure include:

- Ischaemic heart disease
- Hypertension
- Valvular heart disease
- Profound tachy- or bradycardia
- Myocarditis
- Myocardial depression by drugs
- Cardiac tamponade.

Practice point

If you can't identify an aetiology for the cardiac failure, and the ECG is normal, reconsider your diagnosis, but don't forget the possibilities of constrictive pericarditis or diastolic ventricular dysfunction. This latter diagnosis is difficult to make but is more common in elderly hypertensives and can be diagnosed with echocardiography.

When cardiac failure appears, consider what has precipitated it and treat this as well as the failure itself; such precipitating factors include:

- Arrhythmia: tachy- or brady- (e.g. atrial fibrillation, complete heart block)
- Myocardial infarction
- Excess fluid intake (e.g. post-op IV fluids)
- Excess fluid retention (e.g. NSAIDs, acute kidney injury)
- Anaemia, thyrotoxicosis or any precipitating illness, such as infection in the elderly
- Either precipitating drugs or poor medication compliance in a patient on anti-failure drugs.

Rule out the above with the appropriate investigations and correct them if possible.

Case history (continued)

The patient remained breathless despite an initial bolus of furosemide 80 mg. His chest X-ray confirmed that he had pulmonary oedema.

Management

He needs rapid therapy to improve his clinical condition, with acute treatment to correct his breathlessness, followed by further therapy to maintain and improve left ventricular function.

The acute phase of therapy consists of:

- *IV nitrates* (e.g. glyceryl trinitrate 10–200 µg/min titrated to reduce systolic BP by 10–15% and not below 90 mmHg): these provide excellent rapid symptomatic relief by offloading the ventricle, and should be first-line therapy. Continue IV diuretics, initially boluses (e.g. furosemide 40 mg) but he might need a furosemide infusion.
- *IV diamorphine* (5 mg slowly): this not only relieves symptoms, by offloading the ventricle, but is an excellent anxiolytic.
- *ACE inhibitor or angiotensin receptor antagonist*:
 - Start after acute symptoms have settled and patient is haemodynamically stable.

- Remember to watch renal function.
- Use an appropriate dose of ACEIs, or they will be ineffective.
- *Beta blockers:*
 - There is excellent evidence to back their use (e.g. CIBIS II, MERIT) and these should be started as soon as the patient is haemodynamically stable and off IV inotropes and IV vasodilators. There is now evidence to back their use even in patients with severe heart failure. Either carvedilol or bisoprolol is the first-line drug (see starting dose, mentioned above).
 - Up-titration of the drugs must be very gentle (every 2 weeks) and warn patients they might initially feel worse. If their symptoms worsen do not increase the dose; if they continue to worsen, reduce or stop the beta blockers.
- *Spironolactone:* 12.5–25 mg daily should be given to all patients with moderate to severe heart failure (RALES trial); check the potassium because of risk of hyperkalaemia.
- *Digoxin:*
 - Valuable in atrial fibrillation
 - Shown to reduce rate of hospitalisation in patients, not mortality (VA study).
- *Non-invasive positive pressure ventilation (NIV):* patients often respond very well to just CPAP alone, but might need BIPAP. You should be aware that positive pressure ventilation might cause hypotension: monitor the patient appropriately.

Other lifestyle changes

- Reduce alcohol intake
- Reduce weight
- Reduce salt intake
- Take moderate regular exercise.

His breathlessness and pulmonary oedema resolved after 2 days and plans were made to discharge him when his condition was stable.

Practice point

Patients are often left on excessively high doses of diuretics and can easily become dehydrated on discharge unless their therapy is reduced. However, patients developing heart failure while on diuretics usually require to be discharged on a higher dose than on admission.

The trend would be to increase the dose of the ACEI while reducing the diuretic dose, assessing the response by monitoring symptoms, signs and weight. Ideally this should be done by a heart failure clinic; these are often nurse led and excellent for such patients.

Selected points

- Heart failure may be difficult to diagnose – especially with diastolic dysfunction.
- A proportion of elderly patients are on diuretics but have no objective evidence of heart failure (systolic or diastolic).
- Echocardiography should be performed in all patients to identify an aetiology.
- ACEIs should be given to all patients unless contraindicated (i.e. renal impairment, aortic stenosis, renal artery stenosis).

Information

- Systolic heart failure is associated with a decreased left ventricular ejection fraction. The heart is enlarged and there is frequently accompanying diastolic heart failure. The cause is often IHD.
- In diastolic heart failure there is normal left ventricular systolic function with a small heart and impaired left ventricular filling. It often occurs in the elderly associated with hypertension. At present there are no data from large trials on treatment of diastolic failure but the expert consensus opinion at present is that it should be treated in the same way as systolic failure.

- **Progress.** This 80-year-old man was treated according to the algorithm in Fig. 10.11. He made a gradual recovery but was unable to go home. He was placed in a nursing home but was readmitted with pulmonary oedema again and died.

VALVULAR HEART DISEASE

Aortic stenosis

In the UK, the most common cause of aortic stenosis in the elderly is degenerative calcific disease; in younger patients it is more often on the basis of a congenital bicuspid valve. Although it is now less common, do not forget rheumatic heart disease as a cause.

Case history (1)

A 75-year-old man is brought to hospital after he had blacked out when running for a bus. He had fully recovered when he reached hospital.

Cardiac examination revealed normal pulse, with normal rhythm and BP 180/90. The heart sounds were soft with an ejection systolic murmur heard all over the praecordium.

The CXR was normal and the ECG showed LBBB.

A clinical diagnosis of **aortic sclerosis** was made. The house officer has seen him and has asked you to review him.

How should you manage him?

- You **must** admit him to MDU; you need to quantify the severity of his aortic stenosis with an echocardiogram.
- Patients with severe aortic stenosis have a very high 1-year mortality.
- If he has severe aortic stenosis he should be referred for consideration of aortic valve replacement as an inpatient.
 - **Progress.** His echo showed him to have a gradient across the aortic valve of 70 mmHg with good LV function and he had an aortic valve replacement on that admission without complications. He was well at follow-up 18 months later.

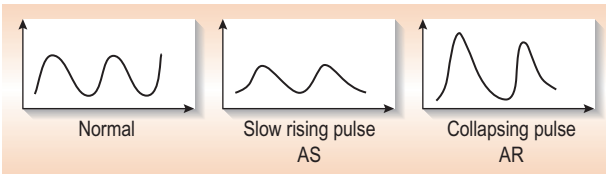


Figure 10.15 Pulse patterns in aortic valve disease.

Remember

If in doubt refer for echo *and* cardiac assessment.

Practice points

In aortic stenosis, the physical signs can be misleading and do not necessarily correlate with its severity:

- Post-exercise syncope in someone with a systolic murmur is suggestive of significant aortic stenosis.
- A diagnosis of aortic sclerosis should not be made without full echo assessment.
- Soft heart sounds in the context of an aortic murmur often suggest significant stenosis.
- Although the pulse might be useful in diagnosing aortic valve lesions (Fig. 10.15), you should note that in elderly patients the pulse might not be reduced because of loss of arterial tree elasticity.
- Severe aortic stenosis with symptoms needs referral for inpatient surgery.
- Elective aortic valve replacement of aortic stenosis is associated with a very low mortality and is excellent curative surgery for symptomatic aortic stenosis with good ventricular function.

Aortic regurgitation (AR)

There are many causes of aortic regurgitation, including both valve and aortic root disease. Degenerative disease, rheumatic disease, congenital valvular diseases and infective endocarditis are some of the more common causes.

Remember

In acute AR (e.g. endocarditis) the murmur might become inaudible and be replaced by a third heart sound. If this happens the patient needs *urgent* surgical referral.

Practice points

In aortic regurgitation the physical signs do tend to correlate with its severity, i.e. the worse the lesion, the more marked the collapsing pulse, the wider the pulse pressure and the longer the murmur:

- Echocardiography to quantify the severity and left ventricular size and monitor these parameters on a regular basis thereafter.
- When the ventricle begins to dilate, referral for consideration of surgery is necessary.
- Medical therapy with an ACE inhibitor may delay the time until surgery is needed.

Mitral valve disease

Case history (2)

A 64-year-old man was admitted in heart failure with signs of mitral regurgitation. He had been in hospital 6 months earlier with heart failure and had been well since then on maintenance medical therapy including an ACE inhibitor. He had cardiomegaly on chest X-ray but the ECG showed no ischaemic changes. Echo assessment confirmed papillary muscle dysfunction causing posterior valve leaflet prolapse with resultant severe MR; the left ventricle was dilated and had some impairment of function. Cardiac catheterisation showed normal coronary arteries and confirmed the echo findings. He had an intra-operative TOE and then mitral valve repair and made a good recovery.

In mitral regurgitation, the underlying cause must be adequately treated; this alone can cause a marked improvement in the severity of the MR. Surgery should be considered in all patients with functional disability (despite adequate medical therapy) and/or worsening LV function documented by echo. The threshold for surgery is constantly dropping with improving technique. Outcome often depends on LV function, so refer early. All patients with MR should be discussed with a cardiologist to arrange appropriate follow-up, investigation and surgical referral.

When should you consider surgery in valvular disease?

- *Aortic stenosis*: this is usually well compensated but deterioration is rapid once symptoms have developed. Refer for operation if dyspnoea, chest pain or syncope. *Note*: as an inpatient if stenosis is severe.
- *Aortic regurgitation*: refer for operation when LV starts to dilate (end systolic dimension > 5.5 cm).
- *Mitral stenosis*: refer for opinion when symptoms uncontrolled on medical treatment. Remember percutaneous valvuloplasty may be a first-line option. Generally when the valve area < 1 cm² then intervention is needed.
- *Mitral regurgitation*: progressive symptoms despite medical therapy and/or LV dilatation.

Remember

Age is not a barrier to valvular surgery if LV function is good and no major coronary disease is present.

Prosthetic valve problems (*all these should be referred to a cardiologist urgently*)

- Heart failure: must be assumed to be due to valve malfunction until proved otherwise.
- Murmurs: paraprosthetic leaks common but should be formally assessed by urgent echo followed by TOE.
- Infection: blood cultures must be taken for any febrile illness before giving antibiotics. Endocarditis of prosthetic valve should be referred to cardiothoracic centre.
- Anti-coagulants: control is essential (INR 3.5). *Always* take specialist advice before any surgical intervention. *Do not stop a patient's warfarin or reduce the dose until he/she is fully anti-coagulated with IV heparin.*

INFECTIVE ENDOCARDITIS

Infective endocarditis is an endovascular infection of cardiovascular structures, including cardiac valves, atrial and ventricular endocardium, large intrathoracic vessels, and intracardiac foreign bodies e.g. prosthetic valves, pacemaker leads, and surgical conduits. The annual incidence in the UK is 6–7 per 100 000, but it is more common in developing countries. Without treatment the mortality approaches 100% and even with treatment there is a significant morbidity and mortality.

Untreated infective endocarditis is invariably fatal. Delay in the diagnosis of infective endocarditis might:

- Make medical treatment more prolonged
- Increase the risk of death
- Promote the need for surgery which might have been avoided had treatment been started earlier.

It follows that endocarditis is a diagnosis that needs to be kept in mind when dealing with any pyrexial or constitutional illness in patients with valvular or congenital heart disease.

Remember

The main problem with endocarditis is delay in the diagnosis. *Never* delay empirical antibiotic therapy; take the appropriate cultures and start treatment.

Diagnosis is made using the modified Duke criteria (Table 10.6).

Case history

One of your colleagues hands over a patient who has just been admitted. He is a 28-year-old man who presented with a pyrexia and history of feeling unwell for 6 weeks. His doctor had prescribed amoxicillin for a flu-like illness 3 weeks previously. He has a pyrexia of 38.5°C and looks unwell. There is a mid-systolic murmur radiating to the neck and the apex. Careful inspection of the nail beds showed some splinter haemorrhages. Blood cultures were taken in A&E on arrival. Your colleague wants you to look these up tomorrow and, depending on the results, start antibiotics.

Table 10.6 Modified Duke criteria for endocarditis*

Major criteria

- ← A positive blood culture for infective endocarditis, as defined by the recovery of a typical microorganism from two separate blood cultures in the absence of a primary focus (*viridans streptococci*, *Abiotrophia* species, and *Granulicatella* species; *Streptococcus bovis*, HACEK† group, or community-acquired *Staphylococcus aureus* or enterococcus species); or
- ← Persistently positive blood cultures, defined as the recovery of a microorganism consistent with endocarditis from either blood samples obtained more than 12 hours apart or all three or a majority of four or more separate blood samples, with the first and last obtained at least 1 hour apart; or
- ← A positive serologic test for Q fever, with an immunofluorescence assay showing phase 1 IgG antibodies at a titre >1:800; or
- ← Echocardiographic evidence of endocardial involvement
 - ← an oscillating intracardiac mass on the valve or supporting structures, in the path or regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation; or
 - ← an abscess; or
 - ← new partial dehiscence of prosthetic valve; or
- ← New valvular regurgitation.

Minor criteria

- ← Predisposition: predisposing heart condition or intravenous drug use
- ← Fever: temperature $\geq 38^{\circ}\text{C}$ (100.4°F)
- ← Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, Janeway's lesion
- ← Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
- ← Microbiological evidence: a positive blood culture but not meeting a major criterion as noted above, or serological evidence of an active infection with an organism that can cause infective endocarditis‡
- ← Echocardiogram: Findings consistent with infective endocarditis but not meeting a major criterion as noted above.

*The diagnosis of infective endocarditis is definite when: (a) a microorganism is demonstrated by culture of a specimen from a vegetation, an embolism, or an intracardiac abscess; (b) active endocarditis is confirmed by histological examination of the vegetation or intracardiac abscess; (c) two major clinical criteria, one major and three minor criteria, or five minor criteria are met.

†HACEK denotes haemophilus species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

‡Excluded from this criterion is a single positive blood culture for coagulase-negative staphylococci or other organisms that do not cause endocarditis. Serologic tests for organisms that cause endocarditis include tests for *Brucella*, *Coxiella burnetii*, *Chlamydia*, *Legionella*, and *Bartonella* species. After Raoult D, Abbara S, Jassal DS, Kradin RL. Case records of the Massachusetts General Hospital. Case 5-2007. A 53-year-old man with a prosthetic aortic valve and recent onset of fatigue, dyspnea, weight loss, and sweats. NEJM 2007.

What do you do and what else do you want to ask the patient?

- If you have good clinical grounds for a diagnosis of endocarditis you must start empirical treatment, as soon as you have taken at least three sets of cultures (from different sites). You take blood for a full blood count and a further blood culture *now* so that he can have his first dose of antibiotics without delay.
- You will ask him if he has had any recent dental work, if he is an IV drug user or if he has ever been told he has a murmur (pre-existing lesion).
- You will send off baseline U&Es, CRP, ESR, urinalysis and microscopy and get an ECG.

While taking the cultures you ask him a few questions and he tells you someone mentioned he had a murmur when he was a child but nothing further was done. He also tells you he had root canal work 8 weeks ago. You start him on a slow injection of benzylpenicillin (1.2 g, to be given 4-hourly thereafter) and gentamicin (80 mg 12-hourly) for the first 2 weeks. You must subsequently discuss anti-microbial therapy with a microbiologist.

His cultures subsequently show he has *Streptococcus viridans* in all sets of cultures and his echo shows a vegetation on a bicuspid aortic valve but no significant gradient (stenosis) or regurgitation.

- **Progress.** He makes an uneventful recovery on 2 weeks IV therapy penicillin 1.2g 4-hourly + gentamicin 80 mg² 12-hourly followed by oral penicillin for a further 4 weeks.

What advice and follow-up do you give him?

You tell him prophylactic antibiotic therapy is unnecessary for dental procedures unless there is an infective process already present.

A few practical points

- Prosthetic valve endocarditis is very difficult to manage and must be referred to a cardiothoracic surgical centre.
- Haemodynamic deterioration might precipitate the need for surgery in endocarditis. The difficulty is that operative results are clearly better if the surgeons can wait to allow adequate antibiotic therapy to enable them to operate in a field that is no longer infected. However, in some cases this might not be possible because fatal haemodynamic deterioration can only be prevented by early surgery.
- Endocarditis often needs surgical intervention. *Always* involve the cardiologists as soon as possible.
- Transthoracic echocardiography does not always exclude a diagnosis of endocarditis and TOE will often help; the cardiologist will give appropriate advice.
- Development of first-degree AV block strongly suggests an aortic root abscess, hence the need for regular ECGs in all cases.
- A fever as a result of antibiotic sensitivity can develop after a prolonged course of intravenous antibiotics (especially penicillins). This can lead to a false suspicion that the endocarditis is not successfully treated: always liaise closely with the microbiologist.
- Always discuss cases that are either not responding or worsening with the surgeons, via the cardiologist.

- Right-sided endocarditis is a disease characteristic of intravenous drug users. The condition presents with cardiac signs such as a murmur or evidence of tricuspid regurgitation on the JVP. However, there might be few signs at the outset and the major abnormality could be on the chest X-ray, with areas of apparent consolidation suggestive of a bronchopneumonia. The condition can present with a 'white-out' of the two lung fields.

Remember

Always involve the cardiologist early in patients with endocarditis.

Further reading

Thuny F, Grisoli D, Collart F et al. Management of infective endocarditis: challenges and perspectives. *Lancet* 2012; **379**: 965–975.

PULMONARY HYPERTENSION

Case history (1)

A 54-year-old woman presents with increased breathlessness over 2 weeks. She is a heavy smoker with a chronic productive cough. She recently developed a cold, followed by a cough with purulent sputum and increased breathlessness.

On examination she is cyanosed and tachypnoeic at rest. Her pulse is 120/min, irregularly irregular (atrial fibrillation).

Her JVP is raised 5 cm. She has a systolic murmur at the left sternal edge with an enlarged pulsatile liver and bilateral leg and ankle oedema.

On examination of her chest she had generalised wheezing with bilateral basal crackles.

Investigations

ECG confirms atrial fibrillation with right ventricular hypertrophy.

Chest X-ray shows evidence of **pulmonary hypertension** with prominent pulmonary arteries.

Echo shows enlarged right ventricle. Doppler shows PA pressure to be 28 mmHg.

- **Diagnosis.** Cor pulmonale – pulmonary hypertension, secondary to COPD.

Pulmonary hypertension/cor pulmonale

Pulmonary hypertension/cor pulmonale is defined as fluid overload secondary to lung disease in hypoxic patients with COPD. Pulmonary hypertension can be present for years without causing symptoms.

Cor pulmonale is enlargement of the right ventricle secondary to increased afterload due to primary lung disease in patients who have no

other cause of ventricular dysfunction. Symptoms include worsening exertional dyspnoea, fatigue and chest pain. On examination JVP is raised and there is a right ventricular parasternal heave, a loud pulmonary component of the second heart sound, fluid retention and peripheral oedema.

Pathophysiology of cor pulmonale

Pulmonary hypertension leads to the elevation of right ventricular pressure and dilatation of both the right ventricle and the right atrium. This leads to the physical findings of peripheral oedema, raised JVP, hepatic enlargement (which might be pulsatile because of the tricuspid regurgitation) and ascites. The cause of the fluid retention in cor pulmonale is still debated because there is little evidence that it is truly due to haemodynamic dysfunction of the right ventricle. The most likely explanation is that hypercapnia – an almost invariable feature of cor pulmonale – interferes with the humoral mechanisms controlling sodium and water balance, leading to fluid retention.

In practice, it is relatively common to encounter patients in whom there is evidence of fluid retention, right ventricular hypertrophy and left ventricular problems. Presumably this occurs because of coexistent primary problems such as ischaemic heart disease and hypertension.

How would you manage a case of cor pulmonale?

You must treat the underlying disease process, hopefully with the aim of avoiding this final common pathway. Some of these patients are at risk of pulmonary emboli and need anti-coagulation: discuss with the cardiologist. Otherwise, treatment of cor pulmonale is symptomatic, with diuretics for fluid retention. There is not yet any direct evidence of benefit from ACE inhibitors for RV dysfunction alone. However, patients will often have coexisting LV disease that benefits from ACE inhibitors.

In COPD, a PaO_2 of less than 7.3 kPa is an indication for home oxygen treatment. This has been shown to reduce mortality, pulmonary resistance and hypoxia and might produce symptomatic relief.

What is the prognosis?

In COPD, the development of cor pulmonale is always a sinister sign because it invariably represents the final common pathway. The prognosis of cor pulmonale in COPD without treatment is poor (5-year survival is about 30%) compared with treatment (5-year survival of about 60%). Although cor pulmonale is not an invariable feature of COPD, it usually heralds the terminal phase of the illness in those who develop it.

Remember

Patients with long-standing lung disease may develop pulmonary hypertension.

Investigations: cor pulmonale

- Arterial blood gases
- Chest X-ray: showing large pulmonary arteries \pm evidence of underlying lung disease
- ECG: showing right ventricular strain pattern with right axis deviation and often P-pulmonale
- Echo: showing large right ventricle and atrium, tricuspid regurgitation and high PA pressures
- CT chest with contrast: to further delineate underlying lung disease and pulmonary vasculature

- **Progress.** This patient's underlying COPD was treated with bronchodilators, antibiotics and she was told to stop smoking. Her blood gases after recovery from the acute episodes showed PO_2 of 7.1 kPa and arrangements were made for domiciliary oxygen. She was continued on anticoagulation with warfarin and her AF was controlled with digoxin 0.125 mg. She is being followed by the pulmonary rehabilitation nurse and outpatients.

Case history (2)

A 21-year-old man presents with an 8-week history of increasing breathlessness; he is now able to walk less than 20 yards, having previously been able to keep up with his peers at weekly soccer games. He has no past medical or drug history and has never smoked.

On examination he is cyanosed, has a JVP raised to his ears with 'cv' waves, a right ventricular heave, pansystolic murmur at the right sternal edge and peripheral oedema.

His chest X-ray shows strikingly enlarged pulmonary arteries but clear lung fields. His echo shows an enormous right heart with torrential tricuspid regurgitation but no significant left-sided problems.

What is the likely diagnosis and prognosis?

Primary pulmonary artery hypertension is the most likely diagnosis. This is an aggressive disease process with a very poor outlook. Heart-lung transplantation is usually the only chance for survival. Prostacyclin, high-dose calcium channel antagonists, Bosentan (an oral antagonist of endothelin-1 receptors) and sildenafil have all been shown to be of limited benefit as medical therapy.

- **Progress.** This man was assessed in the Transplantation Centre and is now awaiting heart and lung transplantation.

CARDIOMYOPATHIES

A cardiomyopathy is a primary disease of the heart muscle. Generally, these fall into three functional categories: dilated, hypertrophic and restrictive cardiomyopathies.

Remember

- Cardiomyopathies are rare in acute medical practice but don't forget them
- Echocardiography is essential in defining the problem.

Case history (1)

A 42-year-old man is admitted to MAU with increasing breathlessness and signs of pulmonary oedema. There is no history of chest pain or palpitations. He had a severe episode of flu 3 months ago and has since not been able to return to his marathon running. He has never smoked and drinks less than 10 units per week.

On examination he is tachypnoeic. His pulse is 120/min and regular, with blood pressure 100/60. His venous pressure is raised and he has a gallop rhythm on auscultation. He also has bilateral basal crackles but no peripheral oedema. His chest X-ray confirms cardiomegaly and pulmonary oedema.

- **Diagnosis.** Acute heart failure with pulmonary oedema. He is given immediate treatment for this (p. 294).

He has a dilated cardiomyopathy (DCM)

There are a number of causes of dilated cardiomyopathies. The above case history is suggestive of either a post-viral or idiopathic cardiomyopathy. A thorough history, examination and investigations will enable you to rule out many causes of cardiomyopathy, e.g. alcohol-induced cardiomyopathy.

Further investigations show no ischaemia on the ECG and global ventricular systolic dysfunction on his echo. Cardiac MR shows dilatation. Viral titres to enteroviruses are positive.

Treatment is as for acute heart failure (p. 304). He recovers well and is able to get back to normal after 4 months.

Some tips on the management of dilated cardiomyopathies (DCMs)

- In principle, the treatment is the same as treatment of heart failure but you should get cardiology input early for advice on specialist investigations and further treatment.
- Define an aetiology if possible, as this might identify a reversible/treatable cause, e.g. alcohol excess:
 - An echo is essential
 - An endocardial biopsy might be helpful.

- It is possible to make a complete recovery from a dilated cardiomyopathy, especially those of viral aetiology (remember to check viral titres).
- Some acute DCMs run an aggressive course with rapidly worsening ventricular function, and cardiac transplantation might be required. Surgically implanted left ventricular assist devices (LVADs) are becoming increasingly common as a bridge to either recovery or transplantation.

Remember

Ischaemic heart disease can present as a dilated cardiomyopathy; it can respond well to treatment with secondary prevention and, where appropriate, revascularisation.

Case history (2)

You are a junior doctor in clinic and you see a new GP urgent referral. She is a 35-year-old woman who presented to the A&E department with syncope and palpitations. She was noted to have a soft systolic murmur. She was sent home by A&E as her palpitations had settled and her ECG was thought to be normal. The GP has asked you to see her because she is concerned as the patient's sister, age 28, dropped dead whilst ironing. Her ECG shows left ventricular hypertrophy with an S in V1 of 21 mm plus an R wave in V6 of > 35 mm (see [Figure 10.17](#)).

What are you concerned about?

Hypertrophic cardiomyopathy

This is an autosomal dominant condition with variable penetrance. There is disorganisation of myocytes and myofibrils, which often results in ventricular hypertrophy that most often affects the septum. The septal hypertrophy can cause left ventricular outflow obstruction, resulting in symptoms such as exercise-induced syncope. The main risk with which you should be concerned is that of sudden death.

Some practice points for hypertrophic cardiomyopathy (HCM)

- On echo (which all patients must have) cardinal features include: asymmetrical septal hypertrophy, systolic anterior motion of the mitral valve and an outflow gradient.
- The degree of outflow obstruction and hypertrophy do not reliably correlate with risk of sudden death.
- Screening of family members and referral to a geneticist are essential because certain HCM mutations are associated with a higher risk of sudden death. Don't forget, HCM can be sporadic as well as hereditary.
- Beta blockers are the mainstay of medical therapy but amiodarone can be useful. However, certain patients will benefit from an automatic implantable cardioverter defibrillator (AICD).

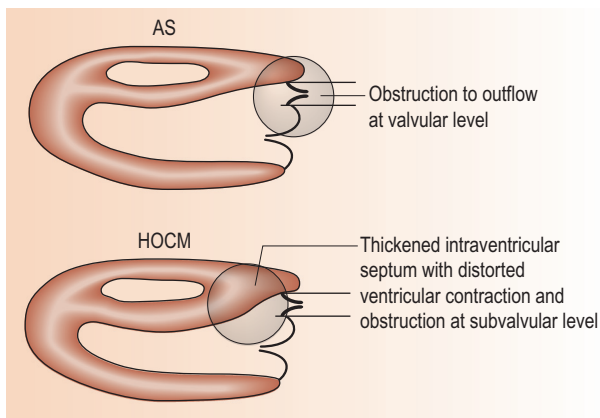


Figure 10.16 The difference between aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM).

- Patients with outflow obstruction might benefit from septal reduction by either percutaneous alcohol ablation or surgical myomectomy.
- Sometimes, differentiation of HCM from aortic stenosis can be difficult (Fig. 10.16; Table 10.7) – get specialist advice!
 - **Progress.** This patient was treated with β blockers but had further episodes of syncope. She has been fitted with an ICD.

HYPERTENSION (HT)

Case history (1)

An anxious 33-year-old woman comes to A&E with a bad migraine. Her BP has been recorded as 180/120 on a number of occasions while she is waiting to be seen by the medical team.

How will you assess her?

First you need to decide on the significance of the BP reading:

- Relevance of anxiety: a raised BP is a common response to stress, more so in some individuals than in others. 24-h ambulatory BP monitors can be of help in these situations.
- Prior history of high BP: adds significance to the present reading.
- Presence of family history of hypertension (HT): probably the single most useful determinant in essential HT.
- Relationship to migraine: no direct link between this and HT has been established.
- Relationship to age: BP does rise with age, but still carries an adverse cardiovascular risk. The WHO International Society of Hypertension

Table 10.7 Differentiation of aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM)

	AS	HCM
Murmur	Ejection systolic	Ejection systolic
		May be additional MR murmur
Pulse. Additional heart sounds	May be slow rising	Described as jerky fourth sound possible (associated with double apical pulsation)
ECG	LVH in later stages may be normal even when severe	LVH (including early stages) May be bizarre changes including large septal Q waves
CXR	Heart size may be normal even when severe	Heart size may be normal
Echo	Aortic valve thickened	Characteristic:
	Gradient on Doppler across valve	1. Asymmetric septal hypertrophy
		2. Systolic anterior motion of mitral valve
	Left ventricular hypertrophy if severe	3. Mid-systolic closure of aortic valve

classify hypertension as a systolic of > 130 mmHg and a diastolic of > 85 mmHg

- Relationship to lifestyle: high alcohol intake, obesity and lack of exercise are common contributory factors in patients with high BP.

What should you be looking for?

- Clinical signs of end organ damage:
 - Fundoscopy: hypertensive retinopathy grades I–IV
 - LVH: forceful/displaced apex beat, loud A2
 - Proteinuria.
- Causes of secondary HT:
 - Coarctation of the aorta: have you felt the femorals, especially in the young patient?
 - Renal disease: renal bruits/proteinuria/urea and electrolytes
 - Cushing's syndrome: obesity, striae; might have low K^+
 - Conn's syndrome: no signs; usually low K^+ and high normal Na^+
 - Pheochromocytoma: presentation often atypical (e.g. acute pulmonary oedema, sweating attacks) rather than textbook flushing/palpitations.
- Baseline investigations:
 - U&Es, eGFR and glucose: look for electrolyte imbalances (e.g. Conn's, renal disease and diabetes)

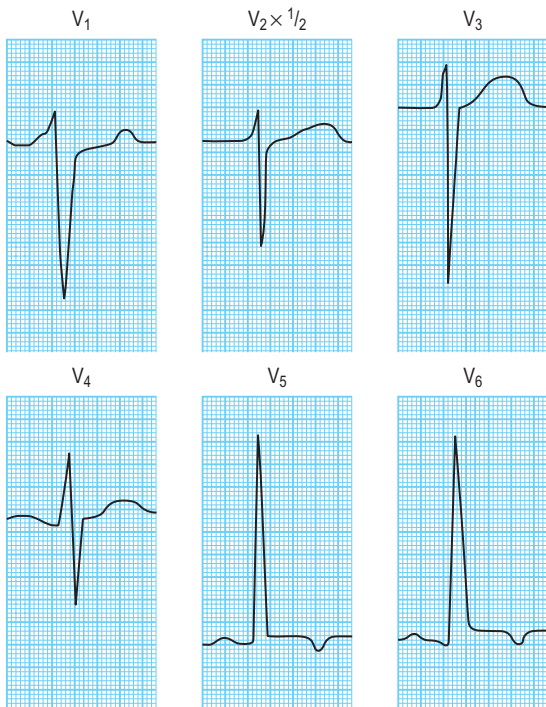


Figure 10.17 ECG showing left ventricular hypertrophy (S in V₂ + R in V₅ > 35 mm).

- ECG: a very insensitive detector of LVH but when voltage criteria are present this carries considerable prognostic risk and should not be ignored. **Figure 10.17** shows LVH with S in lead V₂ and R in V₅ more than 35 mm
- CXR: cardiomegaly might be present but rarely adds much to good clinical examination (rib notching exciting, but coarctation should not have been missed clinically!)
- Echo: a more sensitive indicator of LVH.

When should you look for secondary causes?

- Young patient (under 45) and no family history of hypertension.
- HT resistant to treatment or those with accelerated HT.

Investigations in this group include:

- Renal ultrasound: non-invasive, readily available, excludes major renal pathology.
- Isotope renogram (+ captopril stress): reasonable screening test for renal artery stenosis but not very sensitive (might miss some).

- Magnetic resonance angiography (MRA) with contrast will give a definitive diagnosis in renal artery stenosis. Although renal angiography is the gold standard this tends to be used only when intervention (renal angioplasty) is considered.
- 24-h urine collection: catecholamines and cortisol: these require separate bottles! Plasma catecholamines are most accurate for phaeochromocytoma, if available.
- CT/MRI abdomen: when adrenal disease suspected/confirmed + CT, MRI angiography for reno-vascular disease.

Remember

- High BP is a significant risk factor for future cardiac events and should be followed up, especially in diabetics
- Secondary causes apart from renal disease are rare – but you will see a few cases.

- **Progress.** This patient's hypertension was treated with candesartan 8 mg daily. Her BP fell to 160/100 and therefore bendroflumethiazide 2.5 mg daily and amlodipine 5 mg daily have been added to her treatment. She was also prescribed a statin. Her BP is now controlled at 140/85.

Case history (2)

A 50-year-old man is visiting from Ghana and is brought to A&E by his relatives after behaving oddly. His BP is recorded by the nurses as 220/140 in both arms. This is **accelerated hypertension**.

What is your immediate management?

Clinical assessment:

- CNS: orientation, focal neurological signs (differentiation of hypertensive encephalopathy and a small stroke might be difficult).
- Fundi: haemorrhages/exudates and/or papilloedema indicate accelerated hypertension.
- LVH: clinical and ECG. Most patients with severe HT have ECG evidence of LVH.
- Urinalysis to look for renal disease and diabetes.
- Remember to look for secondary causes and treat as appropriate.

Investigations

- Renal function: renal impairment likely in severe HT and may be accompanied by electrolyte disturbance
- CT head scan: if focal signs present to exclude stroke

What drugs are available for treatment in this case?

- Oral:
 - ACE inhibitors (Fig. 10.18)
 - Diuretics, e.g. thiazides
 - Calcium channel blockers, e.g. nifedipine, diltiazem.
- Intravenous treatment (labetalol, nitroprusside) should be reserved for a real emergency, e.g. aortic dissection, when minute-to-minute control is needed. But lower BP *cautiously*.
- In this man, a reasonable approach would be 10 mg capsule of nifedipine intrabuccally, which will gradually reduce his BP over the next half an hour or so.

Information

- Lowering BP is crucial in the management of accelerated HT. Be cautious, because of the risks of causing a stroke if you lower BP too quickly
- Very high BP readings can occur in an ischaemic stroke and should be treated *very cautiously* because of the risk of extending the stroke

Long-term treatment of hypertension

Do not forget non-pharmacological measures, including weight loss, diet, stopping smoking and regular exercise; these are often glossed over and can have a significant impact. Current practice includes all major classes of anti-hypertensive drugs as first-line therapy. The ANBP2 trial showed that diuretics were as effective as any other treatment for first-line therapy. However, in many patients an ACE inhibitor would be a sensible choice. Remember, strict control is of paramount importance in diabetic patients.

Side effects of anti-hypertensive medication that might present acutely to hospital

- Beta blockers:
 - Asthma
 - Symptomatic bradycardia (especially in the elderly)
 - Cardiac failure
 - Masking of hypoglycaemic symptoms
 - Worsening of peripheral vascular disease symptoms.
- Diuretics:
 - Gout
 - Hypokalaemia (if severe, i.e. < 2.5 mmol/L: consider Conn's syndrome)
 - Diabetes (often overlooked).
- ACE inhibitors:
 - Cough (often overlooked)
 - Hypotension/falls (especially in the elderly)
 - Renal failure (especially in diabetics and claudicants where renal artery stenosis is more common).
- Calcium channel blockers:
 - Non-dependent ankle oedema (especially nifedipine, amlodipine)
 - Constipation (especially verapamil).

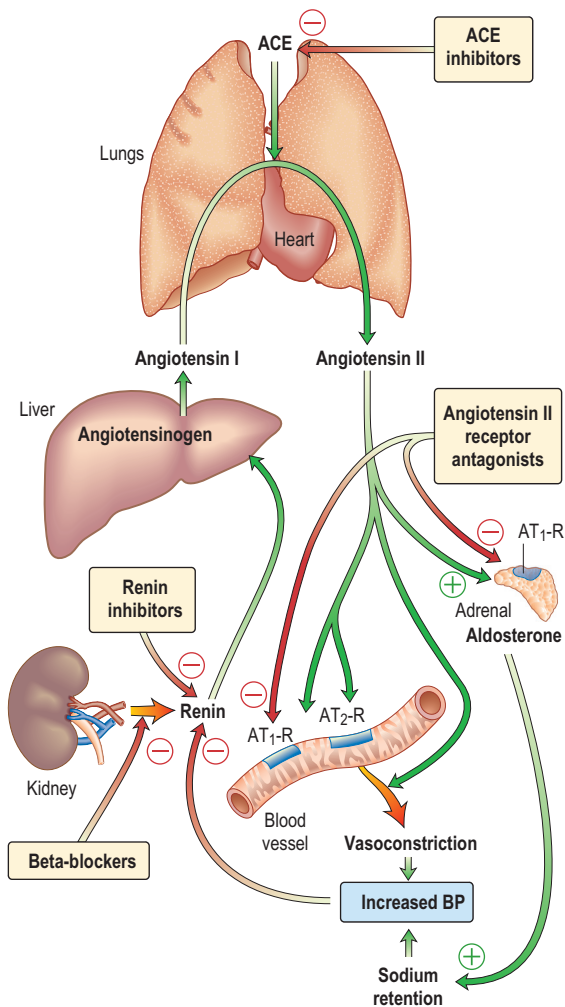


Figure 10.18 The renin–angiotensin–aldosterone system. ACE, angiotensin-converting enzyme.

- **Progress.** This patient was started on lisinopril 5 mg daily, increasing to 15 mg over 3 weeks, along with bendroflumethiazide 2.5 mg daily. Six months later the BP was still not adequately controlled at 150/88 and he has just been started on aliskerin (a renin inhibitor).

THE SWOLLEN/PAINFUL LEG

Common causes of a swollen leg include:

- Deep venous thrombosis (DVT)
- Acute rupture knee joint/Baker's cyst
- Trauma, e.g. rupture of tendon/muscle
- Infection: cellulitis, osteomyelitis.

Case history (1)

A 36-year-old woman on the oral contraceptive pill developed pain in her left calf 3 days ago; it had become increasingly swollen since. Examination revealed oedema of the lower leg without any change in colour or prominence of the veins; there was tenderness along the line of the deep veins. Doppler studies showed early thrombus in the popliteal veins. She was anti-coagulated with heparin and warfarin for 6 months and given alternative contraceptive advice.

Many hospitals now have an excellent DVT service run by specialist nurses.

Investigation of DVT

- D-dimer assay:
 - Has a high negative predictive value, i.e. if low (< 500 ng/mL), a DVT is unlikely
 - Is often used in conjunction with a clinical risk score to decide if a patient needs treatment and ultrasonographic studies.
- B mode venous compression ultrasound: is generally the first-line investigation of choice. It detects clot reliably only in popliteal/femoral vein, not in calf veins. However, 30% of patients with calf vein clots will have an extension and anti-coagulation is now recommended.
- Venography: although probably the gold standard, can be misleading if past history of venous thrombosis and is no longer used as first-line investigation.

Treatment

The patient should be started on subcutaneous LMWH and continued until formal anti-coagulation with warfarin is at target level; current recommendations for warfarin are:

- 6 months: proximal DVT ± pulmonary embolus
- 3 months: localised calf DVT (6 weeks is probably enough for a first DVT with no persisting risk factors).

Target INR is 2.5. With recurrent DVT, screening for thrombophilia is necessary.

Dabigatran, a direct thrombin inhibitor, is now being used as it does not require therapeutic monitoring.

Case history (2)

A 78-year-old man developed sudden pain and weakness of the left hand. The hand was cold and pulseless indicating **acute limb ischaemia**. He was in sinus rhythm but a systolic murmur was noted at the apex. Successful embolectomy was performed. Echocardiography showed a mass in the left atrium, which proved at surgery to be an atrial myxoma and was removed.

Some practical points

- AF (even when paroxysmal) is the most common cause of embolisation but do not forget rare causes such as endocarditis, ventricular thrombosis and atrial myxoma.
- If you suspect a peripheral embolus involve the vascular surgeon early as minimising time to embolectomy is as vital as 'door to needle' time in an MI.
- In the patient with acute abdominal pain and AF, whom the surgeons say is not 'surgical', do not forget mesenteric ischaemia.
 - **Progress.** This patient's hand recovered following embolectomy. He was left with a mild sensory loss. He has had no further problems.

ACUTE BREATHLESSNESS

Case history (1)

You are called by the nurses to see a 63-year-old man who has become breathless. As you walk over to the ward you consider what the causes might be on this rather scanty history.

Remember

Respiratory diseases can cause breathlessness within minutes or hours, or slowly over days, weeks or months.

The systems involved would most probably be cardiac or respiratory. You go through the list in [Box 11.1 \(p. 346\)](#) as you walk to the ward.

Despite the long list, the chances are that this 63-year-old man has COPD, chest infection or heart failure; or, if the onset was sudden, a pulmonary embolus.

Initial assessment

- What does the patient look like? Is he in shock?
- What is the severity of the problem?
 - Tachypnoea?
 - Is the patient using his accessory muscles?
 - Is there any respiratory distress?
 - Colour: is the patient cyanosed?
- Pulse: rate, type, volume?
- BP?

Then make a full cardiac and respiratory examination. Is there any evidence of DVT?

This vague history shows the vast diagnostic possibilities, shown in the table but a shorter differential diagnosis can be made in context of the age of the patient, the past medical history and the current clinical situation. This man turned out to have **heart failure**.

- **Progress.** He was treated with furosemide 40 mg daily and 3 days later, he was discharged with follow-up with his own doctor.

Upper airways obstruction

Case history (2)

A 29-year-old male had been at a party where he had consumed a lot of alcohol. He managed to get home with the help of his friend but he then vomited and fell to the floor. He was holding his throat and had great difficulty in breathing. The friend realised that he was in great distress and called an ambulance.

Diagnosis: Upper airways obstruction

THIS IS AN EMERGENCY!

- Stridor
- Respiratory distress
- Cyanosis ± shock.

Fortunately, the emergency crew recognised the problem and tried to clear the airway. There was no improvement so the Heimlich manoeuvre was performed and a large bone was expelled with immediate relief of the man's respiratory distress. He was taken to A&E for assessment but discharged after 2 hours.

Remember

The **Heimlich manoeuvre** is used to expel an inhaled foreign body:

- Stand behind the patient
- Encircle the upper part of the abdomen, just below the patient's rib cage, with your arms
- Give a sharp, forceful squeeze, forcing the diaphragm sharply into the thorax.

This should expel sufficient air from the lungs to force the foreign body out of the trachea. If this fails, urgent assessment by experienced ENT or cardiothoracic clinician is required. Fibre optic or rigid bronchoscopy will be required if obstruction beyond vocal cords.

Other causes of upper airway obstruction are shown in [Table 11.1](#), all of which require emergency management, which is also shown.

COUGH

Cough is common and when persistent can cause considerable fear and distress. Apart from the immediate discomfort of coughing, paroxysmal cough can interrupt sleep, provoke retching or vomiting and, if severe, result in rib fractures or syncope. Always enquire about sputum and its colour.

Table 11.1 Causes of upper airways obstruction (with management strategies)

Cause	Action
Anaphylaxis: laryngeal oedema	Adrenaline (epinephrine) 0.5 mg IM Antihistamine, e.g. chlorphenamine 10–20 mg by slow IV injection Hydrocortisone IV 100 mg slowly O ₂
Carcinoma of upper airway	Call ENT for laryngoscopy
Tracheal compression, e.g. bleeding post-thyroidectomy	Tracheal decompression, e.g. release skin sutures
Inhaled foreign body	Heimlich manoeuvre

Case history

A 67-year-old man is admitted to hospital with a myocardial infarct. Following successful coronary intervention he is discharged on anti-platelet therapy, atorvastatin and enalapril. When seen again 2 weeks later, he was very well but complained of a persistent hacking cough. This had been keeping him awake at night.

In this case, as the patient has only a cough and is not breathless, the cause is very likely to be the **ACE inhibitor (enalapril)**. This should be stopped and an ACE receptor antagonist, e.g. vasartan started. Unlike ACE inhibitors, angiotensin receptor antagonists do not affect bradykinin metabolism and do not produce a cough.

Cough is provoked by stimulation of mucosal and stretch receptors of the lung. Accordingly it has a number of causes:

Acute cough

- Inhalation of direct irritants, e.g. smoke, chlorine gas, ozone and other air pollutants.
- In the asthmatic, inhalation of specific allergen, e.g. pollen or non-specific low-concentration irritants, e.g. perfume, tobacco fumes.
- Upper and lower respiratory tract infections (yellow/green sputum).

Chronic cough

- Large airway obstruction, e.g. carcinoma of bronchus or inhaled foreign body (*Note:* peanuts and other inhaled food will not be radio-dense).
- Persistent bronchial inflammation, e.g. asthma, bronchiectasis, COPD, smoking.
- Persistent infection, e.g. tuberculosis, lung abscess.
- Interstitial lung disease, e.g. pulmonary fibrosis, asbestosis.
- Raised left atrial pressure, e.g. mitral stenosis, left ventricular failure.
- Gastro-oesophageal reflux (GORD) and bulbar dysfunction.
- Iatrogenic, e.g. ACE inhibitors, radiation pneumonitis.

Enquire about associated features

- Haemoptysis
- Pleuritic pain
- History of myocardial infarction (suggesting cough is due to left ventricular failure)
- Post-nasal drip.

Investigations

All patients with persistent cough should have a CXR

Other investigations will depend on the likely cause, e.g. serial peak flow in asthma, contrast studies if gastro-oesophageal reflux or aspiration is suspected and sputum culture, including request for *Mycobacterium tuberculosis* isolation if the cough is productive.

BREATHLESSNESS AND WHEEZE

Asthma causes breathlessness, cough and wheeze. However, all that wheezes is not asthma.

Information

- Asthma provocation tests might be required to exclude mild-moderate and variable bronchial irritability
- Bronchoscopy will be required in all chronic cases remaining undiagnosed

Differential diagnosis of asthma:

- COPD:
 - Patient usually > 40 years of age
 - Heavy smoker > 20 pack years. (*Note:* patients with asthma might also smoke)
 - History of variable wheeze: in patients with asthma, chest wheeze is usually worse at night and may only be episodic.
- Upper airway obstruction with stridor:
 - Occurs when there is a mechanical obstruction in the larynx or trachea
 - Is heard during inspiration and expiration; but inspiratory sound when mouth open is most typical
 - Might be associated with vigorous accessory muscle activity and obvious distress.
- Left ventricular failure (LVF):
 - Acute LVF can be difficult to differentiate from asthma
 - Nocturnal symptoms common to both.

Figure 11.1 shows causes and triggers of asthma.

Information

Causes of stridor:

- Tumour
- Foreign body
- Bilateral vocal cord palsy
- Laryngeal oedema
- Thyroid goitre

Case history

A 24-year-old female was admitted to MAU with breathlessness for 6 h. She has had a 'cold' for 2 days. Past history revealed her being 'chesty' as a child. It was noticed that she could not complete sentences easily. Heart rate was 126/min and respiratory rate was 30/min. There was expiratory wheeze over the lung fields. This patient has **severe acute asthma**.

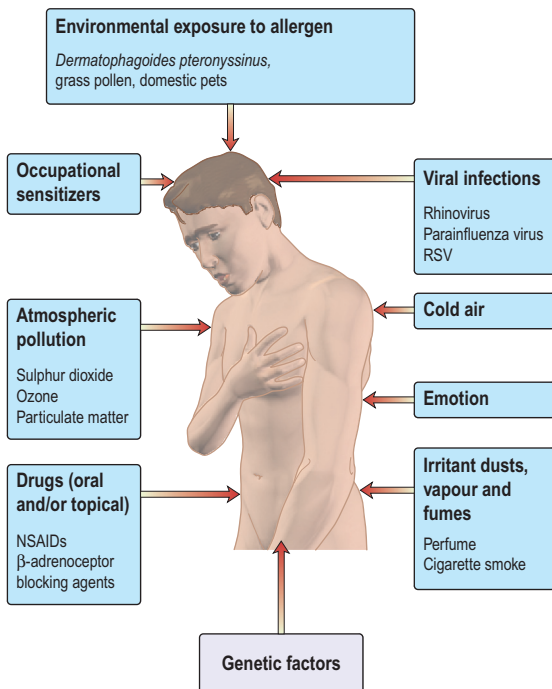


Figure 11.1 Causes and triggers of asthma. RSV, respiratory syncytial virus; NSAIDs, non-steroidal anti-inflammatory drugs.

Remember

Severe acute asthma:

- Increased breathlessness/cannot complete sentences
- Respiratory rate > 25/min
- Heart rate > 100/min
- PEFr 30–50% of best
- Arterial oxygen saturation (SaO₂) < 92%

How would you manage this patient in A&E?

Immediate management should be:

- Reassurance that treatment will be effective
- Oxygen 40–60% (Keep SaO₂ > 90%)
- Nebulised short acting β_2 agonist (SAB), e.g. salbutamol 5 mg or terbutaline 10 mg) with oxygen. (NB only 10% of drug reaches the lungs)
- Systemic corticosteroids:
 - Prednisolone 30–40 mg daily or
 - IV hydrocortisone 200 mg 8-hourly
- Monitor SaO₂ by oximetry
- Arterial blood gases (ABGs):
 - Initially if SaO₂ < 90%
 - Re-check (2-hourly) if PaO₂ < 8 or PaCO₂ > 5 kPa until the PaCO₂ is stable and the saturation is >90%
- PEFr 4-hourly. *Note:* performing PEFr might be distressing for patient: do not demand unnecessary repeat testing
- ECG
- Chest X-ray.

30 min later there has been no significant improvement in her breathlessness and PEFr. What would you do next?

- Call for senior help.
- Continue with nebulised β_2 agonist, now with added ipratropium (500 μ g). Repeat every 30 min if necessary.
- Intravenous aminophylline infusion can be used if patient does not respond to repeated nebulisation with β_2 agonist and ipratropium. However, *do not use this* if oral aminophylline has been taken.

Information

	Normal range	
<i>Analysis</i>	<i>S-I units</i>	<i>Non S-I units</i>
PaO ₂	12–15 kPa	90–113 mmHg
PaCO ₂	4.5–6.0 kPa	34–45 mmHg
Hydrogen ions	37–45 nmol/L	pH 7.35–7.43
Bicarbonate	24–28 mmol/L	24–28 mEq/L

Information

IV aminophylline:

- Ensure patient is not on oral theophylline (do not give aminophylline if patient is on oral aminophylline)
- Monitor BP and heart rate
- Loading dose 250–500 mg over 1 h

Infusion:

- 1 mg/kg over 4 h
- 0.5 mg/kg/h thereafter
- Check aminophylline level at 6–8 h after the start of infusion and adjust dose

Other therapy

- Intravenous β_2 agonist, e.g. salbutamol 3–20 $\mu\text{g}/\text{min}$ is an alternative in most cases.
- Magnesium sulphate 1.2–2 g IV infusion over 20 min with cardiac monitoring.

Remember

Life-threatening acute asthma

- Silent chest, feeble respiration, cyanosis
- Bradycardia/hypotension, arrhythmia
- Exhaustion/confusion
- PEFr < 33% of best
- Arterial oxygen saturation < 92%.

Indications for HDU or intensive care

Presence of life-threatening features and:

- $\text{PaO}_2 < 8$ on 60% oxygen
- $\text{PaCO}_2 > 6$ kPa
- Previous history of requiring ventilation.

Remember

- Beware of the SILENT CHEST!
If asthma is very severe, air entry will be minimal and breath sounds quiet or absent.

There is now improvement in PEFr and breathlessness with nebulised β_2 agonist and ipratropium. What treatment should be offered to her now?

Continuing management should be:

- Keeping $\text{SaO}_2 > 90\%$ with oxygen supplementation
- Corticosteroids: prednisolone 20–40 mg daily, on a reducing dose
- 2–4-hourly nebulised short acting β_2 agonist (SABA) therapy.

When could she be discharged?

The patient can be discharged when:

- Symptoms, particularly nocturnal symptoms, have improved
- Ideally, PEFR should be 75% of best and diurnal variation (i.e. 'morning dips') < 25%. If patient is improving and compliance expected to be good, an earlier discharge is reasonable.

24–48 h before discharge

- Add inhaled corticosteroids, e.g. beclometasone, to oral steroids.
- Replace nebulised bronchodilators with inhalers.
- Introduce long-acting inhaled β_2 agonists, e.g. salmeterol.
- Check inhaler technique (? might need spacer).
- Determine the cause of this attack (non-compliance, infection, allergen exposure).

Talk to asthma nurse

At discharge, patient should have:

- Oral and inhaled corticosteroids and long acting inhaled β_2 agonist (LABA). SABAs can be used on an 'as required' basis.
- Peak flow meter and diary.
- Management plan if condition deteriorates.
 - **Progress.** This patient was discharged after 7 days on treatment as above. She requires close follow-up because of the severe acute attack.

Discharge letter to GP should include:

- Admission and discharge PEFR
- Recommended GP follow-up in 1 week
- Asthma clinic follow-up, preferably within 4 weeks.

Further reading

British Thoracic Society Guidelines for asthma 2009. www.brit-thoracic.org.uk

HYPERVENTILATION

Case history

A 15-year-old schoolgirl is brought by her teacher to the A&E department with dizziness and feeling faint. You notice that she is anxious, sighing and has erratic ventilation. There are no other physical signs on examination. Her teacher volunteered that the girl was anxious about impending examinations.

What should you do?

Full examination, CXR, PEFR or spirometry, and arterial blood gases (even if oximetry is normal).

You have decided that her symptoms are due to hyperventilation. This should be confirmed by demonstration of a respiratory alkalosis with a low PaCO_2 and $[\text{H}^+]$ in the arterial blood. Reassure the patient and ask her

to breathe into a closed paper bag: when settled she can be discharged with further reassurance. *Note:* mild asthma is a common provocative cause and might require further investigation.

Hyperventilation syndrome refers to a condition of recurrent attacks of anxiety, sometimes phobic in nature, and provoking such profound hyperventilation to cause a reduction in arterial $p\text{CO}_2$ that tetany occurs. Other features include perioral and digital paraesthesia, carpopedal spasm, muscle weakness, dizziness and a sense of impending loss of consciousness or fear.

An attack of hyperventilation can be induced by a strong emotional experience in otherwise normal individuals, e.g. witnessing an accident.

In many patients, the label of hyperventilation syndrome is inappropriately given when mild asthma or other conditions, such as heart failure, lie behind the respiratory sensation. Indeed, hypocapnia resulting from hyperventilation might further provoke bronchoconstriction.

Clinically obvious hyperventilation can also result from a metabolic acidosis and will be recognised by arterial blood gas analysis: a reduced pH and bicarbonate contrary to the alkalosis of respiratory hyperventilation.

Tetany: see p. 451; overbreathing can cause tetany (p. 451).

- **Progress.** This patient settled quickly. She was reassured that there was nothing seriously wrong with her. She was taken home to her parents with a pamphlet explaining the hyperventilation syndrome.

HAEMOPTYSIS

Case history

A 63-year-old male smoker presents with a 4-month history of cough. Recently he has been coughing up blood in his sputum. He has also been breathless on exertion.

Coughing up blood is a dramatic symptom and can be frightening to patients and their families.

Colour of blood – this can differ with different causes

- Pink frothy sputum: pulmonary oedema.
- Rusty sputum: pneumonia.
- Make sure it is not haematemesis, which would be suggested by:
 - History of retching
 - Altered blood (resembling coffee grounds)
 - Low pH of contents.

Enquire about epistaxis, which may cause confusion. Blood-stained saliva suggests bleeding from gums.

Common conditions presenting with haemoptysis

- Carcinoma of the bronchus:
 - Smoker
 - Age > 40 years
 - Usually abnormal chest X-ray.

- Pulmonary embolism:
 - Risk factors for DVT
 - Chest X-ray often negative
 - History of acute breathlessness.
- Pulmonary tuberculosis:
 - More common in Asian people (in the UK), people drinking alcohol in excess, patients with HIV infection
 - Age often < 40 years
 - Chest X-ray usually shows patchy opacities in the upper lobes.
- Bronchiectasis:
 - History of purulent sputum and/or possibly recurrent haemoptysis over years
 - Cystic lesions on chest X-ray at lung bases in some but not all patients
 - High-resolution CT scan of the lungs is diagnostic, with bronchial dilation, loss of airway tapering at the periphery, bronchial wall thickening and thickening and cysts at the end of the bronchioles
 - Bronchiectasis is also a feature of cystic fibrosis.

Remember

- Chest X-ray might be normal, e.g. pulmonary embolism
- Large opacity: consider malignancy or tuberculosis.

Less common causes of haemoptysis are:

- Vasculitis (both the following are ANCA positive):
 - Granulomatosis with polyangiitis (Wegener's)
 - Microscopic vasculitis.
- Pulmonary haemorrhage:
 - Goodpasture's syndrome
 - Idiopathic pulmonary haemosiderosis.
- Chronic venous congestion of lungs:
 - Mitral stenosis
 - Left ventricular failure.
- Aspergilloma: seen in association with cavitary lung disease.

Management of this case

A chest X-ray was taken (Fig. 11.2 and Information box) which showed a pleural effusion and a hilar mass. The pleural effusion was aspirated and sent for cytology. A pleural biopsy was taken under ultrasound control and showed no evidence of malignancy on histology.

Video-assisted thoracoscopy was then performed and this allowed visualisation of the pleura. A biopsy taken showed a **squamous cell carcinoma**.

The patient was referred to the multidisciplinary team for discussion of treatment options.

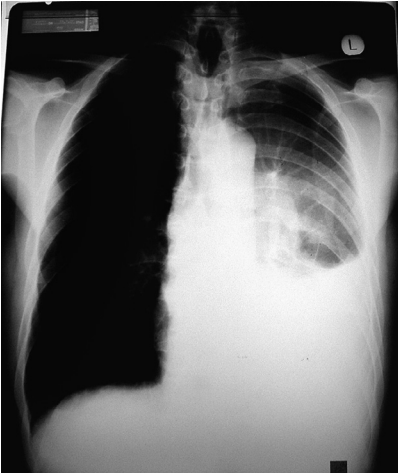


Figure 11.2 Chest X-ray showing a left pleural effusion and a hilar mass.

Information

Chest X-rays

A standard chest X-ray (CXR) is taken posteroanteriorly (PA), with the patient facing the X-ray plate; the beam is directed at the patient's back at a standard distance.

An emergency department film is often taken anteroposteriorly (AP), with the patient lying down (supine) on the X-ray plate; the beam is directed at the patient's front – the distance from X-ray source can vary.

In an AP:

- Heart size and mediastinum are magnified.
- Pleural effusion which lies along back of chest cavity when patient supine might be missed.
- Film quality may be poor.

Don't request an AP 'portable' film unless it would be unsafe for the patient to have a PA film.

Management of massive haemoptysis

As little as 250 mL can fill the bronchial tree and be life threatening. Happily, this is uncommon but nevertheless frightening for everyone involved:

- Monitor: oxygen saturation with oximetry, blood pressure and pulse rate.
- Perform CXR. Exclude coagulation defects.

- Endotracheal intubation and suction might be required.
- Urgent bronchoscopy by an experienced doctor is sometimes required.
- A cuffed tube can be employed to protect the unaffected lung. It is inserted into the bronchus via a bronchoscope.
- Bronchial artery embolisation is highly effective if the bleeding vessel can be identified.

Information

Massive haemoptysis can occur in the following conditions:

- Tuberculosis
- Bronchiectasis
- Aspergilloma
- Carcinoma of the bronchus

Remember

Only a minority of patients have a malignant cause of massive haemoptysis.

CHEST PAIN

Diagnosing the cause of a chest pain is often difficult; it can be straightforward or take days to diagnose correctly. A careful history (eliciting site, character and radiation of the pain) is often more useful than tests:

- Exercise-induced central chest pain is usually cardiac in origin.
- Rest pain might be: cardiac, pleuritic, musculoskeletal, nerve root irritation, oesophageal, mediastinal or referred pain from abdomen.
- Lung diseases only cause pain if the pleura, mediastinum, intercostal nerves or bones are involved.

Is it cardiac pain?

See also p. 284.

Central chest pain: radiates to arms and neck. Dull ache, severe heavy 'constricting' character. May be associated with breathlessness.

Typical angina

Occurs on exercise and is eased by rest.

Acute coronary syndrome

Pain at rest or on minimal exertion, sometimes very severe with sweating; pain persists.

Pericarditis

Dull or sharp, central, eased by sitting forwards, may be worse with breathing.

Aortic dissection

Severe sudden onset, might be described as 'tearing' pain in the back or anterior chest; patient often shocked.

Is it pleurisy?

Sharp pain in the sides of the chest, which 'catches' with breathing. This is often accompanied by fever, cough \pm sputum or haemoptysis, indicating underlying lung disease.

Think of:

- Pneumonia and pleurisy
- Pulmonary infarction/embolism
- Pneumothorax
- Malignant invasion of pleura.

Is it musculoskeletal?

- Trauma:
 - Rib fracture: 'point' tenderness
 - Crushed vertebra: pain often referred around the chest.
- Chronic pain:
 - Osteoarthritis (OA): long history with acute episodes. Look for spinal deformity
 - Rib or spine disease: might be metastatic cancer; local tenderness and swelling, lumps, history of cancer.
- Muscles: Bornholm's disease. Follows an upper respiratory tract infection; a low-grade fever can occur. Ache in muscles. Might be tender. Definite cases rare.
- Costochondral junction: Tietze's disease; local pain on pressure over junctions. Responds to NSAIDs.

Is it nerve root irritation?

- Typically in a dermatome distribution around the chest. Might be unilateral.
- Vertebral OA, osteomyelitis, prolapsed disc.
- Malignant nerve root compression.
- Herpes zoster (shingles): is there a vesicular rash? (pain may precede rash).

Is it oesophageal?

Reflux causes retrosternal burning pain, usually after food. Worse lying flat and eased by antacid. Can be severe and mimic myocardial infarction.

Oesophageal rupture

Central pain with shock. Might have associated pleural effusion. Occurs after severe vomiting or more commonly endoscopy at which dilatation has been performed for a malignant lesion.

Is it referred pain from outside the chest?

Diaphragm irritation may cause shoulder tip pain. Localisation might be difficult for the patient. Several abdominal emergencies might have chest pain with or without abdominal pain.

Think of:

- Acute cholecystitis
- Acute duodenal ulceration
- Subphrenic abscess
- Perforated bowel

- Peritonitis
- Pancreatitis.

Is it genuine?

Yes – nearly always. Exclude organic disease in *all* cases.

A tiny minority might be attention seeking or have psychiatric disease. Even patients with Munchausen's syndrome might have genuine disease.

What tests do you need to do for chest pain?

After a good history and examination do (as a minimum):

- ECG – repeat if first ECG normal
- CXR
- Serum cardiac markers
- Full blood count, including ESR and CRP.

Many diagnoses will now be obvious but remember:

- A normal ECG does not exclude cardiac pain.
- A normal CXR does not exclude pulmonary embolism.

If still in doubt:

- Retake the history, re-examine the patient and consider unusual causes
- Is WBC or ESR raised?
- Is the patient pyrexial?
- Arrange further investigations, e.g. CT, MR scan.

RESPIRATORY FAILURE

Respiratory failure ($\text{PaO}_2 < 8 \text{ kPa}$) is a common medical emergency often presenting with non-specific symptoms such as mild confusion or agitation. Recognition requires arterial blood gas (ABG) analysis (see below). Oximeters that estimate arterial oxygen saturation from the finger or ear lobe are useful in assessment or monitoring.

Oximeters might be falsely reassuring in the patient breathing oxygen. Importantly, they will not detect alveolar hypoventilation, producing high pCO_2 .

Remember

All breathless patients should have oximetry checked at triage in A&E.

Respiratory failure commonly results from either a problem with the respiratory pump or because of intrinsic lung disease.

Remember

All unconscious patients should have ABG analysis at initial assessment.

With respiratory pump failure the arterial $p\text{CO}_2$ (PaCO_2) is raised. You should think of:

- Severe air-flow limitation, e.g. COPD
- Neurological depression, e.g. coma, sedatives, overdose
- Chest wall problem, e.g. flail chest, pneumothorax
- Neuromuscular disease, e.g. Guillain-Barré, old poliomyelitis.

In intrinsic lung disease (apart from COPD) hypoxaemia is often combined with a reduced PaCO_2

The hypoxaemia arises primarily from a mismatch of ventilation and perfusion in the pulmonary alveolar bed. Hypoxic stimulation of ventilation, coupled with abnormal respiratory sensation, then leads to a reduced arterial $p\text{CO}_2$ (alveolar hyperventilation). A raised PaCO_2 indicates impending respiratory arrest as it suggests either a reduction in ventilatory effort or failure of the respiratory pump.

In hypoxaemia with reduced PaCO_2 , consider

- Infection, e.g. pneumonia
- Shock, e.g. sepsis, hypovolaemia, acute lung injury
- Asthma
- Cardiac disease, e.g. LVF, pulmonary hypertension
- Pulmonary embolism.

In respiratory failure arterial blood gas sampling is necessary to

- Assess severity
- Identify type, i.e. alveolar hypo- or hyperventilation
- Appreciate the degree of compensation (i.e. the chronicity of the condition)
- A coexisting metabolic acidosis commonly causes confusion and can be recognised by the base excess value (see below).

Information

ABG sampling is painful. Contrary to common belief, the use of local anaesthetic does not make the procedure more difficult. Heparin has a low pH and should be expelled from the syringe. Heparin-bonded microsamplers are available and small-diameter needles make local anaesthetic unnecessary. When taking ABG samples it is essential to note the inspiratory O_2 concentration (FiO_2).

Summary of acid-base changes (Fig. 11.3)

In a respiratory acidosis

Carbon dioxide clearance is reduced – there is alveolar hypoventilation. The PaCO_2 and $[\text{H}^+]$ rise. The HCO_3^- is also increased due to renal compensation.

Examples: exacerbation of COPD, flail chest injury, Guillain-Barré syndrome.

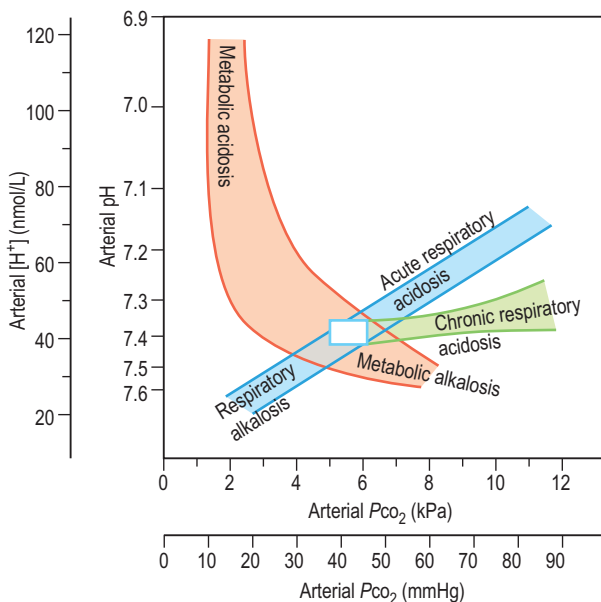


Figure 11.3 The Flenley acid–base nomogram. The bands show the 95% confidence limits representing the individual varieties of acid–base disturbance. The central white box shows the approximate limits of arterial pH and $p\text{CO}_2$ in normal individuals.

In a respiratory alkalosis

There is alveolar hyperventilation and both the PaCO_2 and $[\text{H}^+]$ are decreased. The HCO_3^- is slightly decreased. Examples: acute asthma, anxiety attack.

In a metabolic acidosis

There is disturbance of bicarbonate regulation or excessive H^+ production. The HCO_3^- is reduced and the PaCO_2 falls because of respiratory compensation.

Example: diabetic ketoacidosis, renal failure, shock.

In a metabolic alkalosis

The HCO_3^- is increased and relative hypoventilation leads to a small compensatory increase in the PaCO_2 .

Example: excessive vomiting, profound hypokalaemia.

Normal blood gas values (with F_iO_2 21%):

- pH ~ 7.4
- $\text{PaO}_2 > 10.0$ kPa*
- PaCO_2 4.5–6.0 kPa†
- HCO_3^- 24–28 mmol/L.

*To convert to mmHg, multiply by 7.5.

†The pH changes by approximately 0.1 per 1 kPa change in PaCO_2 .

Information

The base excess value provided by the ABG analyser is calculated by back titration to normal values for PaCO_2 and HCO_3^- .

Common ABG abnormalities

Life-threatening asthma

- pH: 7.2
- PaO_2 : 15.4
- PaCO_2 : 6
- HCO_3^- : 16.2
- BE: -7.3.

Supplemental O_2 is being provided (note the high PaO_2). There is a metabolic acidosis (note the pH and BE) as a result of metabolic demands exceeding O_2 delivery and producing a lactic acidosis. Airflow limitation limits the normal respiratory compensation to this profound acidosis.

Acute or chronic respiratory failure in a patient with COPD

- pH: 7.3
- PaO_2 : 25.8
- PaCO_2 : 12.6
- HCO_3^- : 42.1
- BE: +4.3.

Acute or chronic respiratory acidosis exacerbated by a high F_iO_2 using variable performance mask (40–60% O_2) (note high PaO_2 and PaCO_2). The high HCO_3^- results from renal compensation. The patient was changed to 28% oxygen.

Severe pneumonia (F_iO_2 60%)

- pH: 7.15
- PaO_2 : 4.8
- PaCO_2 : 3.5
- HCO_3^- : 12.5
- BE: -9.3.

Despite high F_iO_2 this patient is hypoxaemic because of ventilation: perfusion mismatch. The profound hypoxia despite oxygen and the associated metabolic acidosis indicate the need for urgent intubation and IPPV and are a reflection of circulatory failure resulting from septic shock.

Management

Respiratory failure can be difficult to assess or manage. Always review the CXR. Discuss with your consultant or other more senior staff. If you feel that the situation is unstable, do not hesitate to call an anaesthetist. Semi-elective intubation is much preferred to a respiratory arrest. It should be performed in the ward before transfer of the patient to the ICU.

How do I recognise impending respiratory arrest?

- Tachycardia > 120
- Tachypnoea, respiratory rate > 30
- Hypotension

- Sympathetic activation: pale and sweaty, agitation, confusion
- Progressive increase in PaCO_2 or fall in PaO_2
- Rapid desaturation on disconnection from O_2 , e.g. when drinking or coughing.

Evaluation is often at the 'end of the bed': is the patient getting tired? Be sensitive to subtle changes or a failure to improve.

Treating the cause

- Individual causes will require different actions: for instance, an intercostal drain for a tension pneumothorax or large pleural effusion (see p. 364).
- In neurological coma, intubation might be necessary for airway protection or to manage raised intracranial pressure by hyperventilation.
- Drug-induced respiratory failure can be confirmed by a therapeutic trial with a specific antidote, i.e. a bolus injection of naloxone for opiates and flumazaniil for benzodiazepines. Infusions will be required if a positive response is obtained as antidotes have short half life.
- Oxygen supplementation should be aimed at raising the PaO_2 to beyond the steep part of the oxygen dissociation curve (Fig. 11.4). Very high PaO_2 values are unnecessary but controlled O_2 therapy via a fixed performance mask is only necessary in chronic respiratory failure resulting from COPD.

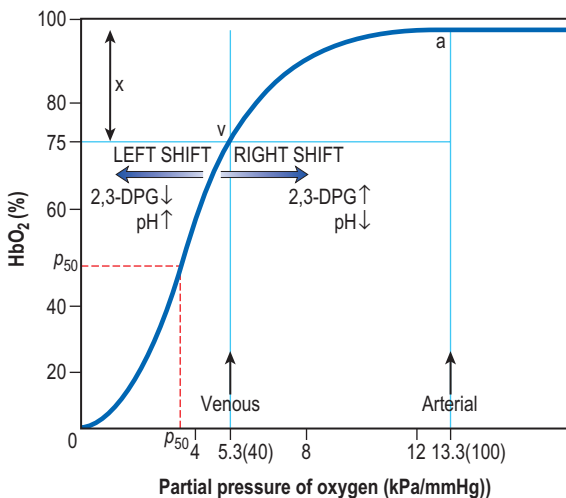


Figure 11.4 Oxygen dissociation curve. BPG, bisphosphoglycerate; a, arterial point; v, venous point; x, arterial venous difference; HbO_2 , oxygen saturation of haemoglobin.

Case history

A 65-year-old man with advanced COPD was admitted with a 1-week history of cough, breathlessness and purulent sputum. In the previous 24 h he had become mildly confused. He was agitated with a respiratory rate of 35, BP 170/90, sweaty with an oximeter reading on air of 72%. There was widespread wheeze and coarse crackles suggestive of retained secretions. ABG analysis revealed pH 7.32, PaO₂ 5.8, PaCO₂ 8.1, and HCO₃ 28.

What do these blood gases mean?

Hypoxaemia with mild acute respiratory acidosis. No evidence of chronic respiratory failure with chronically elevated pCO₂ as HCO₃ is normal, i.e. no compensation.

The initial treatment in A&E was:

- Nebulised bronchodilators (salbutamol 5 mg nebulised + ipratropium bromide 500 µg).
- 28% O₂ by controlled mask.
- IV amoxicillin (erythromycin if patient penicillin allergic).
- IV steroids (this is conventional treatment but there is limited evidence for effectiveness). Hydrocortisone 100 mg × 3 daily.
- Encouragement to clear secretions including sitting patient up and the attention of the physiotherapist.
- CXR to exclude pneumothorax or demonstrate associated pneumonia.

Information

Controlled oxygen via Venturi mask commonly leads to intermittent therapy as the mask is poorly tolerated by agitated, breathless patients. Oxygen via nasal prongs at 1 or 2 L/min is more effective and continuous but is not 'controlled'.

Repeat ABGs were requested: pH 7.20, PaO₂ 6.5, PaCO₂ 12.5, HCO₃ 30.

These results show further CO₂ retention and a deteriorating situation. Oxygen should not be removed – its removal will precipitate severe hypoxaemia. Alveolar ventilation must be increased. Despite using a nasal airway to stimulate cough and aid suction of respiratory secretions there was no improvement. Furosemide was given because it was difficult to exclude coexistent LVF. Intubation was considered appropriate but a trial of non-invasive ventilation (NIV), BiPAP with tight-fitting facial mask was first tried with repeat gases at 1 h. On NIV the respiratory rate slowed and the acute respiratory acidosis resolved.

Non-invasive ventilatory support employs a nose- or face-mask to provide ventilatory assistance to breathing (this is termed 'spontaneous pressure support') or timed breaths ('pressure controlled ventilation'). An

exhalation valve reduces re-breathing. NIV is successful in approximately 70% of patients with respiratory failure resulting from COPD. It should not be employed if intubation would be more appropriate.

Information

Contraindications/cautions to non-invasive ventilation (NIV):

- Unconscious or uncooperative
- Vomiting
- Large amount of respiratory secretions
- Cardiovascularly unstable (beware hypotension)
- Recent facial or upper airway surgery
- Recent upper GI tract surgery
- Inability to protect airway

Mechanical ventilation

In an unstable situation it is essential to maintain oxygenation. As intubation of an acutely unwell patient requires experience, refer to ITU outreach team.

Aims of intubation and mechanical ventilation

- Immediate correction of hypoxaemia
- Slower correction of hypercapnia
- Allow effective suctioning of respiratory secretions.

Hypotension after intubation is very common and relates to

- High airway pressures limiting venous return and causing a fall in cardiac output
- Vasodilation directly caused by sedatives
- A fall in sympathetic tone.
 - *Progress.* This patient was seen by the ITU team who felt, despite his confusion, that he should first be tried on non-invasive ventilatory support. He was put on BiPAP and his blood gases were monitored. These gradually improved on this regimen and antibiotics. He was discharged and advised to see his doctor as soon as he develops a chest infection.

Further reading

- British Thoracic Society. Non-invasive ventilation in acute respiratory failure. Available online: www.thoraxjnl.com
- Roberts, CM, Brown JL, Reinhardt AK et al. Non-invasive ventilation in COPD: management of acute type 2 respiratory failure. *Clin Med* 2008; 8: 517–521.

COPD – ACUTE EXACERBATION

Chronic obstructive pulmonary disease (COPD) is used to describe a number of clinical syndromes associated with destruction of the lung and airflow obstruction.

Case history (1)

A 63-year-old male ex-smoker has had a chronic productive cough for 20 years. For 10 years he has had gradually increasing breathlessness on exertion. His usual exercise tolerance is 200 yards on the flat. One week previously he became breathless on walking between rooms and his sputum became purulent. His normal medication is salbutamol and beclometasone inhalers.

On examination his chest expanded poorly and he was wheezy, but there were no localising signs, no evidence of cor pulmonale or heart failure.

- His usual FEV₁/FVC was 1.9/3.2 (predicted 3.4/4.4) but on arrival was 0.9/2.6
- His CXR showed no acute lesion.

It was decided not to admit him to hospital because:

- He was able to cope at home with aid of his wife
- He was not cyanosed: oximetry showed SaO₂ 97%
- His general condition was good and he had a normal level of consciousness.

He was discharged home with:

- Amoxicillin 500 mg × 3 daily for 1 week
- Prednisolone 30 mg daily for 2 weeks
- Advice to increase his inhaled bronchodilators to salbutamol four puffs, 4-hourly via a spacer
- A follow-up appointment at the chest clinic for 2 weeks.

Key points

- The patient did not need admission because:
 - No evidence of respiratory failure
 - No evidence of cor pulmonale
 - Able to cope at home.
- Antibiotic was broad spectrum and, in particular, covered the majority of *Haemophilus influenzae* and *Streptococcus pneumoniae* organisms (the most common causes of acute exacerbation). Erythromycin was unnecessary because *Mycoplasma* was unlikely.
- Oral steroids were used as adjunct to antibiotics because the patient was already on inhaled steroids and possibly had a degree of steroid responsiveness. This is conventional treatment but there is limited evidence to support it.
- Patient was given a spacer (and shown how to use it) in order to increase the lung deposition of aerosol.
- Salbutamol dose was increased and given 4-hourly because the effect lasts only 4–6 h and is partly dependent on dose.
- Follow-up at chest clinic because patient had moderately severe COPD and had never been assessed:
 - Advise pneumococcal and influenza vaccination
 - Consider referral for pulmonary rehabilitation.

However, the patient's doctor, when seeing the patient 1 week later, cancelled the outpatient appointment believing it unnecessary. He wrote to

the chest physician saying that he was able to manage the patient himself. He had a spirometer in the surgery and when well the patient had an FEV₁ of > 50% predicated normal. Furthermore, the doctor said that the patient:

- Had a definitive diagnosis
- Had only moderately severe COPD
- No cor pulmonale
- No respiratory failure and did not need oxygen
- Did not have bullous lung disease
- Did not have a rapidly declining FEV₁.

The patient's doctor was arranging to perform bronchodilator tests himself using a spirometer and checking the response to both salbutamol and ipratropium inhalers. He would arrange vaccination.

Remember

Spirometry is required to assess the severity of COPD. Most COPD patients can be satisfactorily managed in the community.

Box 11.1. Causes of breathlessness

- Sudden onset:
 - An inhaled foreign body
 - A pneumothorax
 - A pulmonary embolus.
- Breathlessness developing *over a few hours*:
 - Asthma/COPD
 - Pneumonia
 - Pulmonary oedema
 - Respiratory muscle disease, e.g. Guillain-Barré.
- *Intermittent* breathlessness:
 - Asthma
 - Pulmonary oedema
 - Pulmonary emboli.
- Breathlessness *over a few days*:
 - Pleural effusion
 - Carcinoma of the bronchus
 - Pneumonia including pulmonary tuberculosis.
- Breathlessness developing *over months or years*:
 - Fibrosis alveolitis
 - COPD
 - Sarcoid
 - Chest wall or neuromuscular disease
 - Occupational lung disease
 - Non-respiratory causes: anaemia, hyperthyroidism.

Prognosis of COPD

Predictors of a poor prognosis are increasing age and worsening of airflow limitation, i.e. a fall in FEV₁.

Table 11.2 BODE index (Body mass index, degree of airflow Obstruction, Dyspnoea and Exercise capacity)

Variable	Points on BODE index			
	0	1	2	3
FEV ₁ (percent of predicted)	≥ 65	50–64	36–49	≥ 35
Distance walked in 6 minutes (m)	≥ 350	250–349	150–249	≤ 149
MMRC dyspnoea scale	0–1	2	3	4
Body mass index	> 21	≤ 21		

Scores on the modified Medical Research Council (MMRC) dyspnoea scale range from 0 to 4, with a score of 4 indicating that the patient is breathless when dressing.

A patient with a BODE index (Table 11.2) of 0–2 has a mortality rate of 10%; one with a BODE index of 7–10, a mortality rate of 80% at 4 years.

Case history (2)

A 68-year-old female smoker with a chronic productive cough and 5 years of gradually increasing breathlessness on exertion had a usual exercise tolerance of 40 yards on the flat and was breathless bending and washing. She was virtually housebound and lived alone. She developed a cough with purulent sputum and had been breathless at rest for 2 days. She was sent as an emergency to the A&E Department. She was admitted to the medical assessment unit immediately because she:

On examination

- Showed signs of respiratory failure: drowsy and cyanosed, CO₂ flap
- Pulse 130/min; atrial fibrillation; BP 100/60
- Cor pulmonale with tricuspid regurgitation:
 - JVP raised up to the level of the ear
 - Midsystolic murmur at LSE
 - Enlarged pulsatile liver
 - Bilaterally oedematous legs to knees.
- Respiratory rate 30, shallow breaths using accessory muscles of respiration, generalised wheezing and bilateral basal crackles. Investigations showed:
 - Arterial blood gases: pH 7.32, PaO₂ 5.6, pCO₂ 8.2 on air
 - FBC Hb 178 g/L, Hct 54%, WBC 12 300
 - Urea 9.0, K⁺ 3.5, creatinine 102
 - ECG 130 (ventricular rate); atrial fibrillation and right heart strain.
 - Chest X-ray: overinflated lungs with prominent pulmonary arteries (indicating pulmonary hypertension) and normal-sized heart.

Key points

- Patient in respiratory failure with raised PaCO₂: give oxygen via fixed performance mask 24, initially increasing to 28 or 35% if no rise in PaCO₂.
- Cor pulmonale (right heart failure secondary to lung disease) is difficult to improve while the patient remains hypoxic.
- Atrial fibrillation may only be secondary to hypoxaemia and might revert to sinus rhythm when PaO₂ improves.

Immediate treatment

- Oxygen 28% via Venturi mask and repeat ABGs.
- Sit patient upright to help breathing.
- Give nebulised bronchodilators:
 - Salbutamol 5.0 mg with ipratropium 0.5 mg 6-hourly via nebuliser
 - Air rather than high-flow O₂ is safer for nebulising bronchodilators.
- Chest physiotherapy to help sputum expectoration.
- Amoxicillin 500 mg × 3 daily IV until condition improves and then oral for 1 week in total.
- IV hydrocortisone 100 mg × 3 daily until patient improves and then oral prednisolone 20 to 30 mg daily for 2 weeks. If not on oral theophyllines, start aminophylline infusion.
- Monitor oximetry + mental state, respiratory rate and pulse until improvement. Daily weights.

There was no improvement

She was therefore given:

- Doxapram as a respiratory stimulant (1.5–4 mg/min infusion) which sometimes helps.
- Non-invasive intermittent positive pressure ventilation (NIV) (see p. 343). The best technique is using a tight-fitting facial mask to deliver bilevel positive airway pressure ventilation support (BiPAP).

Progress

- Patient more alert
- PaO₂ 8.0, PaCO₂ 8.4, pH 7.35 now on 2 L nasal oxygen
- In sinus rhythm.

Key points

- Oxygen should be prescribed on treatment sheet and given continuously, not 'as required'.
- Management of oxygen is the most helpful and difficult component of treatment.
- Although oxygen by a Venturi mask gives a known concentration it is uncomfortable and claustrophobic. It has to be removed to eat, talk and cough and for nebulised treatment.
- Oxygen by nasal spectacles is more comfortable and can be kept on continuously.
- Nasal oxygen gives variable F_iO₂ depending on pattern of breathing and flow rate between 24% and 35%. It worked on this patient but in many patients with COPD, a 24% oxygen via a mask is preferable when PaCO₂ > 8.0 kPa.

- It takes 30–40 min to equilibrate blood gases with any change in F_iO_2 and blood gases should not be checked earlier.
- It is unnecessary to get the PaO_2 normal: aim to get it at the top of the steep slope of the oxygen saturation curve (see Fig. 11.3).
- If PaO_2 is > 7.5 kPa, a small fall in PaO_2 has little effect on O_2 saturation: this is safe.
- If PaO_2 is 6.5 or less, a small fall produces a dangerous fall in SaO_2 . *Note:* the sigmoid shape of oxygen dissociation curve (see p. 342).
- Increasing the inspired oxygen may cause a small rise in $PaCO_2$ (mostly because of relaxation of hypoxic vasoconstriction in relatively poorly ventilated alveoli). A pH change of < 0.1 or $PaCO_2 < 1$ kPa is not significant, so do not reduce or remove the oxygen.
- If, on increasing F_iO_2 , this patient had not clinically improved and ABGs showed PaO_2 6.8, $PaCO_2$ 12.0:
 - Action: patient still needs oxygen but at a more controlled concentration. Increase F_iO_2 to 35%
 - Get help from senior, preferably from respiratory team and discuss transfer to HDU for non-invasive ventilation or to ITU for assisted ventilation.
 - **Progress.** Over the next few days the patient improved and felt well by 1 week. Her Hb came back as 180 g/L, Hct 55. What would you do now?

Action

Venesect cautiously under Haematology guidance. Three to four units venesected over next few weeks starting before discharge from hospital aiming for a Hct of 50. Continue bronchodilators as inhalers via spacing device, oral steroids continued for 2 weeks and diuretics, e.g. furosemide given.

Key points

- Before discharge blood gases were checked on air and showed a PaO_2 7.0, $PaCO_2$ 6.3. The respiratory nurse was asked to visit to:
 - Discuss disease/risk factors, especially to urge to stop smoking and refer to smoking cessation clinic
 - Explain mechanism of action of drugs
 - Explain use of aerosol devices and spacers
 - Give chest clinic follow-up for 2 weeks.

A follow-up in chest clinic was arranged to:

- Optimise bronchodilator treatment.
- Monitor for polycythaemia and cor pulmonale.
- Assess for long-term domiciliary oxygen (indication $PaO_2 < 7.3$ on two occasions 3–4 weeks apart when patient stable).
- Consider obstructive sleep apnoea in view of marked polycythaemia.

Further reading

British Thoracic Society. Guidelines for COPD. Available online: www.brit-thoracic.org.uk

PNEUMONIA

Pneumonia is an inflammation of the substance of the lungs. It can be classified by site (e.g. lobar, diffuse, bronchopneumonia) or by aetiological agent (e.g. bacterial, viral, fungal, aspiration, or due to radiotherapy or allergic mechanisms). Pneumonias can be community-acquired (CAP; commonest *Strep. pneumoniae*), hospital-acquired (often Gram-negative bacteria) or ventilator-associated (multiple organisms, e.g. *Pseudomonas*, *Klebsiella*, *Acinetobacter*).

Case history (1)

A 33-year-old female non-smoker was admitted to the medical assessment unit with a 2-day history of fever, sweating and cough, productive of yellow, lightly blood-stained sputum. She had pleuritic pain in the left axilla. Herpes labialis was present.

This is the typical history of community-acquired pneumonia.(CAP).

Signs

- Fever 39°C.
- Respiratory rate 28/min.
- Dullness to percussion left lung base; consolidation.
- Bronchial breathing left lung base; consolidation.

Likely infecting organisms

- *Streptococcus pneumoniae*: the most likely cause (35–80% of cases)
- *Haemophilus influenzae*: especially in smokers with COPD
- *Mycoplasma* (4-yearly epidemics)
- *Legionella*
- *Staphylococcus aureus*
- Viral: influenza
- *Chlamydia psittaci*.

Investigations

- Chest X-ray
- Arterial blood gases
- Blood count, WBC + differential
- Urea and electrolytes
- Urinalysis for sugar (is patient diabetic?)
- Blood and sputum culture
- Blood for viral serology and *Legionella*/*Mycoplasma*
- Serology for pneumococcal antigen (blood, sputum and urine)
- Rapid urine test available for *Legionella*

How ill is this patient?

The following CURB-65 criteria indicate the severity of CAP.

CURB-65 Criteria for the diagnosis of severe community-acquired pneumonia

- Confusion*
- Urea > 7 mmol/L
- Respiratory rate ≥ 30 /min
- Blood pressure (systolic < 90 or diastolic ≤ 60 mmHg)
- Age > 65 years of age

Score 1 point for each feature present

Score 0–1 – Treat as outpatient

Score 2 – Admit to hospital

Score 3+ – Often require ICU care

Mortality rates increase with increasing score.

Other markers of severe pneumonia

- Chest X-ray – more than one lobe involved
- $\text{PaO}_2 < 8$ kPa
- Low albumin (< 35 g/L)
- White cell count (< $4 \times 10^9/\text{L}$ or high > $20 \times 10^9/\text{L}$)
- Blood culture – positive

*Confusion is described as a new disorientation in person, place or time.

- **Progress.** This patient was young, previously fit, not breathless or shocked. The chest X-ray (Fig. 11.5) showed a left lower lobe pneumonia and the WBC was 11 500. Normal urea. PaO_2 10.5 kPa.

This pneumonia is not severe on the CURB criteria.

The patient was treated with oral antibiotics and was discharged in 24 hours (see Antibiotic choices, p. 353).

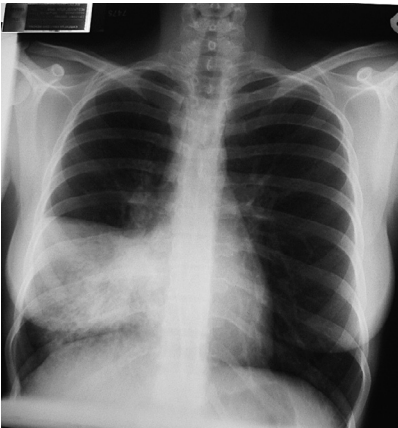


Figure 11.5 Lobar pneumonia.

Case history (2)

A 73-year-old man was brought to A&E by his very anxious wife. He had had winter bronchitis for the last 5 years and was a current smoker of 20 cigarettes/day. One week ago he had the 'flu' and this morning became increasingly breathless, sweaty, pale and confused. He had had a diagnosis of angina made 2 years ago.

Bedside assessment summary:

- Confusion
 - RR > 30/min
 - BP 110/40
 - **73 years old**
 - Dehydrated
 - Pre-existing COPD
 - Pre-existing angina
- i.e. CURB-65 score of 4+ (no blood tests done yet for urea).

Investigations show

- CXR (Fig. 11.6):
 - Diffuse opacification in both lungs
 - Ring opacities in right lung
- Urea 9 mmol/L
- WBC 28 000
- ABG: PaO₂ 9.0 kPa, PaCO₂ 5.3 kPa, on FiO₂ 40%.

This is a high-risk case. He has influenza and a superinfection with *Staphylococcus aureus* causing **severe community-acquired pneumonia** with early abscess formation (ring opacities on the CXR). He needs:

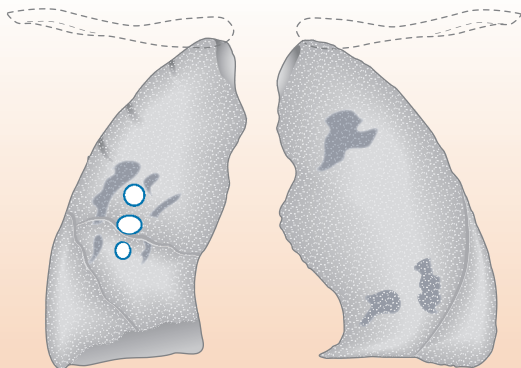


Figure 11.6 Diagram of chest X-ray showing bilateral diffuse opacities and ring opacities in the right lung.

- Rehydration: intravenous fluid
- Intravenous antibiotics: see Antibiotics, below – severe CAP
- Pulse oximetry: give O₂ to try to keep O₂ sat > 90%
- Nursing where he can be easily observed or in an HDU (hourly BP, pulse, RR)
- To be watched for respiratory failure: IPPV might be needed
- Physiotherapy if difficulty coughing up sputum.

Information

Indications for intensive care monitoring and assisted respiration:

- PaO₂ < 8 kPa on 60% O₂
- PaCO₂ > 6.4 kPa
- Patient exhausted, drowsy or unconscious
- Shock
- Hypotension or circulatory failure

Antibiotic choices for CAP

Consult your Hospital Formulary or select from below:

Uncomplicated mild community-acquired pneumonia

- Treat for 5 days with oral medication unless patient not swallowing or not absorbing.
- Oral amoxicillin 500 mg × 3 daily + erythromycin 500 mg × 4 daily (or clarithromycin).
- In penicillin allergic patient with underlying lung disease (*H. influenzae* suspected)
- Clarithromycin 500 mg × 2 daily.

Severe CAP

- IV antibiotics until significant improvement. Co-amoxiclav 1.2 g IV × 3 daily and clarithromycin 500 mg IV × 2 daily.
- Antibiotics for up to 10 days.

Staphylococcal pneumonia

- Treat for 10 to 14 days.
- Flucloxacillin 2 g × 4 daily IV + fusidic acid oral 0.5–1 g × 3 or gentamicin 3.0–5.0 mg/kg IV daily as single dose (check gentamicin levels before second dose).

Legionnaire's disease

- Treat for 3 weeks.
- Clarithromycin 500 mg × 2 daily (for severe cases IV).

Mycoplasma pneumonia N.B.

- Treat for 2 weeks.
- Erythromycin 500 mg × 4 IV or oral daily.
- If allergic to erythromycin give doxycycline 200 mg orally then 100 mg daily or ciprofloxacin 500 mg × 2 daily.

Q fever and psittacosis

- Tetracycline 500 mg × 3 daily for 10 days.
 - **Progress.** This patient made a significant improvement on his IV antibiotics. He was switched to oral antibiotics and made a slow recovery.

Case history (3)

A 24-year-old male, recently arrived in the UK from East Africa, presented with breathlessness of 2 weeks' duration, gradually increasing in severity with a dry cough and sweats. He had a diarrhoeal illness 6 months ago and has recently noticed swollen glands in his neck.

Bedside assessment summary:

- Looks worried
- RR 34/min
- Tachycardia 120 bpm
- Temperature 41°C
- No abnormal signs in chest
- Pre-existing illness: HIV infection
- ABGs: PaO₂ 9.0 kPa; on F_iO₂ 60% PaCO₂ 3.2 kPa
- WBC 23 × 10⁹/L
- Normal serum urea.

You should think this patient may have HIV infection with a *Pneumocystis jiroveci* pneumonia because of country of origin, 6-month history of illness, lymphadenopathy, low white cell count and appearance on CXR (Fig. 11.7).

On investigation, the CXR had:

- Ground glass appearance of lung fields
- Bilateral and perihilar shadowing.

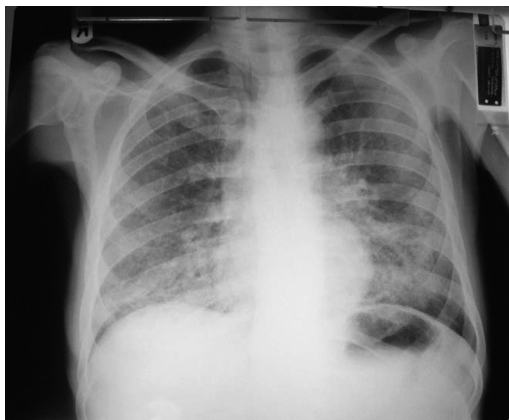


Figure 11.7 Chest X-ray showing bilateral perihilar shadowing. Pneumocystis.

Remember

Other pneumonias

- Heavy alcohol users: inhalation pneumonia (Gram-negative organisms)
- Drug users: 'dirty' needles and syringes, infected emboli to lungs (*Staphylococcus aureus*)
- Tuberculosis: a sputum smear for AFB is quick and easy to do. Can coexist with other pneumonias
- Cytomegalovirus
- Fungal: *Aspergillus*, *Candida albicans*

These latter two are seen in immunocompromised patients, for example with:

- HIV infection
- Leukaemia and lymphoma
- Chemotherapy
- Transplant recipients
- Steroid therapy
- Chronic kidney disease.

Treatment should start in this patient for *pneumocystis jiroveci*

- High-dose IV co-trimoxazole.
- Add IV cefuroxime and erythromycin if in doubt as to cause of the pneumonia.
- Refer to HIV specialist.
- May need high-dose steroids IV if deteriorates.
- Give O₂ to keep O₂ sat > 90%.
- Arrange for induced sputum collection next day.
 - **Progress.** This patient improved on antibiotics and his care was taken over by the HIV team.

Case history (4)

A 68-year-old female smoker was admitted by the surgical team 9 days previously with intestinal obstruction. A laparotomy showed severe diverticulitis with a pelvic mass and a defunctioning colostomy was performed. She has been very slow to mobilise postoperatively and developed a troublesome cough. Two days ago she developed a fever and has now become breathless, tachycardic and has right-sided pleurisy.

Bedside assessment summary:

- Looks ill
- RR 24/min
- Pulse 112 bpm regular
- Temperature 40°C
- Coarse crackles right lung base, patchy bronchial breathing
- Pleural rub

Continued

Case history (4) (continued)

- No evidence of DVT
 - Has vomited recently
 - Recent surgery
 - The surgeons gave her 5 days of IV amoxicillin post-op.
- Her MEWS score (p. 162) has increased to 4.

Investigations

- CXR: patchy opacification right lung base
- ABGs: PaO₂ 7.3, PaCO₂ 4.6
- WBC 16 × 10⁹/L
- Urea 10 mmol/L
- ECG sinus tachycardia

What is the diagnosis?**Severe hospital-acquired pneumonia**

However, for all cases, think of:

- DVT with pulmonary emboli might coexist.
- Inhalation of vomiting causing aspiration pneumonia.
- Previous antibiotics could have selected out Gram-negative organisms.
- Infected intravenous cannulae.
- Pre-existing lung disease – smoker.

Bacteriology in hospital-acquired pneumonia

Wide range of possible organisms:

- Gram-negative bacilli (50%):
 - *Acinetobacter* spp.
 - *E. coli*
 - *Proteus* spp.
 - *Klebsiella* spp.
 - *Pseudomonas* spp.
 - *Haemophilus influenzae*
- Gram-positive cocci:
 - *Staphylococcus aureus*
 - *Streptococcus pneumoniae*
- Anaerobes:
 - *Bacteroides* spp.
 - *Clostridia* spp.

Management

- Give O₂ to raise O₂ saturation to > 90%.
- Rehydrate intravenously.
- Give IV antibiotics to cover wide spectrum:
 - Ceftazidime 2 g × 2 daily and gentamicin 800 mg initially with checks on the blood level.

- If improving after 48 h and able to swallow switch to:
 - Co-amoxiclav (500/125) 625 mg \times 3 daily + oral metronidazole 400 mg \times 3 daily.
- Patient is at high risk of pulmonary emboli: LMW heparin, e.g. Enoxaparin 40 mg SC \times 1 daily if not already on.
- Watch for deterioration.
- Physiotherapy to encourage cough.
 - **Progress.** She responded slowly and was discharged a week later.

LUNG ABSCESS

This is a severe localized suppuration in the lung. The CXR shows cavity formation, often with the presence of a fluid level (not due to tuberculosis).

The causes of lung abscess include aspiration, particularly amongst alcohol users. Lung abscesses also frequently follow the inhalation of a foreign body into a bronchus. They can also occur when the bronchus is obstructed, e.g. a bronchial carcinoma. Chronic or subacute lung abscesses can also follow an inadequately treated pneumonia.

Case history

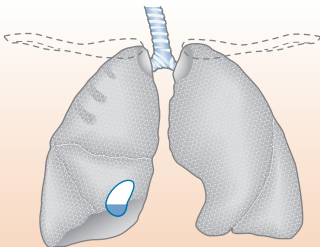
A man of 74 presented with a 1-month history of a productive cough with offensive-tasting sputum, malaise and weight loss. His dentition was very poor. He had just stopped smoking.

On examination he had a temperature of 39.8°C, a few crackles at the right base but no other respiratory signs. A chest X-ray (Fig 11.8) shows a cavity.

Differential diagnosis

- Lung abscess
- Cavitating lung cancer
- Tuberculosis.

Bronchoscopy showed thick secretions in right lower lobe. No bronchial obstruction. Cytology negative.



- Thin walled cavity with fluid level in right lower lobe

Figure 11.8 Diagram of chest X-ray showing a cavity (lung abscess).

Diagnosis: Pyogenic abscess

- **Progress.** The patient responded to antibiotics (cefuroxime and metronidazole) and the abscess resolved in 6 weeks. This probably resulted from aspiration with mouth anaerobes contributing to the unpleasant smell and taste of sputum. Aspiration usually occurs on the right side as the right bronchus is more vertical.

TUBERCULOSIS

Case history (1)

An 18-year-old man who came to the UK 2 years ago from the Indian sub-continent presented with general malaise, photophobia, unproductive cough, weight loss and night sweats.

On examination his temperature was 39.5°C. He looked unwell and appeared rather vague. There was no neck stiffness or any abnormal chest signs.

Investigations revealed Na 120, K 2.6 and urea 2.8, Hb 104 g/L and WBC 6.4; serum ALT and alkaline phosphatase were slightly raised. Portable AP chest film appeared normal.

He was admitted with the diagnosis of **pyrexia of unknown origin**. He had blood and urine cultures and CSF examination. CSF showed an increased cell count, mostly lymphocytes, raised protein and low glucose. No organisms were seen but cultures sent. A departmental PA chest X-ray was performed after 2 days, which showed miliary mottling.

This patient has **miliary tuberculosis with meningitis (TBM)**. It carries a high morbidity if not treated early. The hyponatraemia is dilutional secondary to inappropriate ADH secretion.

- **Treatment.** This is with anti-tuberculous drugs – rifampicin, isoniazid and pyrazinamide. These must commence before cultures are available. Continue for at least 9 months. Ethambutol should not be used because of its eye complications. Corticosteroids, e.g. prednisolone 60 mg are given for the first 3 weeks as they reduce mortality. Relapses and complications (e.g. seizures, hydrocephalus) are common in TBM. The mortality remains over 60% even with early treatment.
- **Progress.** This patient was started on anti-TB therapy as above. His mental state improved and temperature settled. He was discharged after 3 weeks with an appointment in 3 weeks in outpatients.

Case history (2)

A 50-year-old man who was a heavy drinker, with no fixed abode, was brought to A&E 'collapsed'. He had stopped drinking alcohol 1 week previously because he had run out of money. He was confused, hallucinating and coughing, and was transferred to the MAU.

Case history (2) (continued)

On examination he was unkempt and emaciated, confused and jaundiced:

- Temperature: 37.9°C
- Pulse: 100
- BP: 100/60.

On further examination, right upper chest; bronchial breathing + coarse crackles; trachea deviated to the right.

Liver enlarged 3 cm below costal margin. Ascites.

Investigations

- Hb 180 g/L; MCV 106; WBC 8500
- Urea: 1.3
- K⁺: 3.5
- Creatinine: 60, eGFR = 98 mL/min
- Na: 126
- Bilirubin: 40
- Alkaline phosphatase and ALT raised
- Chest X-ray (Fig. 11.9)

A provisional differential diagnosis was made of:

- Delirium tremens
- Pulmonary tuberculosis
- Alcoholic liver disease.

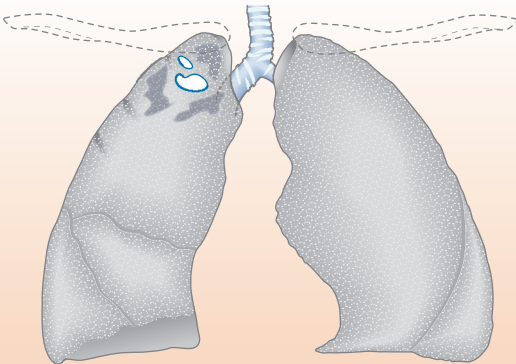


Figure 11.9 Diagram of chest X-ray – patchy opacification with cavitation in right upper lobe. Trachea deviated to the right. Tuberculosis.

Urgent sputum was sent for staining with auramine-phenol fluorescent test and culture + sensitivities for AFB (if no organisms found send at least three more good sputum specimens). TB bacilli were found in the third sputum specimen (smear +ve).

Risk factors for developing TB reactivation

- Heavy alcohol or other drug use
- Diabetes mellitus
- Malnutrition
- Immunosuppression (any cause including steroid therapy).

Management

- Isolate patient as smear +ve.
- Treat delirium tremens (see p. 525). *Note:* always also give thiamine.
- Start anti-TB therapy (see below) as soon as possible.
- Notify patient to infection control and contact TB health visitor to do contact tracing.
 - **Progress.** He was started on anti-TB therapy and treatment for his DTS. He needs directly observed treatment (DOT) because he is unlikely to comply with treatment otherwise. He was also referred to the respiratory and gastroenterological teams.

Case history (3)

A 64-year-old white male smoker was treated by his doctor with antibiotics for bronchitis 3 months ago. As his cough had not resolved, he was admitted to hospital (MAU) 1 week ago. Initial assessment showed a right upper lobe pneumonia and he was treated with oral amoxicillin and erythromycin. Blood and sputum cultures were negative. He had a persistent low-grade fever and the chest X-ray still showed patchy right upper lobe consolidation. You have been called to see him because he has just had a haemoptysis.

Why is this pneumonia slow to resolve?

Consider:

- Obstructing carcinoma of right upper lobe bronchus:
 - Is there a hilar mass?
 - Should he be bronchoscoped?
- Unusual infecting organism.

Further history

Always worth retaking the history.

- His mother was treated for pulmonary tuberculosis in 1941. He was seen in a chest clinic as a child but does not think that he had drug treatment. He has no recall of having BCG vaccination and does not have a BCG scar.
- Pulmonary TB is a possible diagnosis.
- Look carefully at a new PA chest X-ray (Fig. 11.10).

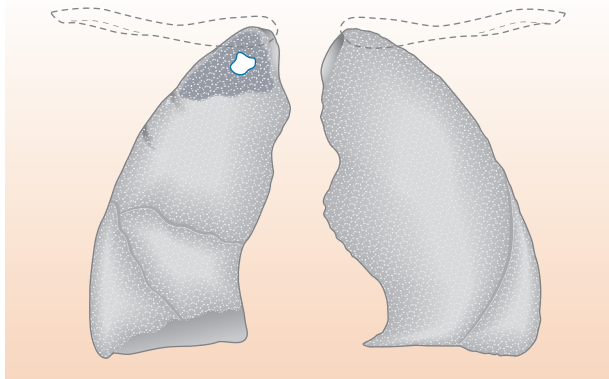


Figure 11.10 Diagram of chest X-ray – right upper lobe consolidation with small apical cavity – probably obscured by the clavicle on previous chest X-ray.

Action

This is TB until proved otherwise.

- Send urgent sputum for auramine staining and TB culture.
- Send at least three sputum specimens.
- Check blood count, liver function, renal function.

Results

The microbiologist calls you urgently:

- The patient has AAFB seen on sputum smear.
- Sputum is being cultured for TB.
- Culture results will be available in 6–8 weeks.
- Sensitivities perhaps not for 12 weeks.

Progress and action

This patient was isolated in a side room (smear +ve).

- Treatment for TB given (see below).
- TB is a notifiable disease in the UK and allows contact tracing to be initiated.

Case history (4)

A 34-year-old Ugandan refugee presented to A&E with high fever, diarrhoea and weight loss. She omitted to inform the staff that she had been found to be HIV positive 6 months previously (with a CD count of 250) and had declined further investigation or treatment at that time.

On examination she appeared unwell, cachetic and was coughing continuously.

Continued

Case history (4) (continued)

- CXR: right lower lobe shadowing and possible right hilar lymphadenopathy
- Hb 75 g/L; WBC 4.2; lymphocytes 0.8; platelets 156
- Na⁺ 128; K⁺ 2.5; urea 11.8; albumin 18.

Blood, stool, sputum and urine cultures were taken and she was admitted to the medical assessment unit and commenced on amoxicillin and erythromycin. She failed to improve and after 3 days the antibiotics were changed to ciprofloxacin, although sputum culture was unhelpful. On day 5 the microbiologist was consulted: examination of sputum for AFB was positive and subsequently *Mycobacterium* TB was isolated from blood and stool.

Key points

- Many patients do not volunteer their HIV status.
- You must indicate that *Mycobacterium* TB is a possibility when requesting sputum examination.
- Atypical radiological changes are common in TB in the immunocompromised.
- Both *Mycobacterium intracellulare avium* and *Mycobacterium tuberculosis* can be isolated from stool and blood.
- A patient from Africa with pneumonia should be admitted to a side room until TB has been excluded.
- The risk of TB developing in those infected (i.e. disease reactivation) in HIV increases when CD count < 200.
 - **Progress.** This patient was started on anti-tuberculous therapy. She was taken over by the HIV team and had continued care from the respiratory team for follow-up and contact tracing.

Treatment – drug therapy in tuberculosis

- Rifampicin: if body weight < 50 kg, 450 mg daily; if body weight ≥ 50 kg, 600 mg daily.
- Isoniazid: 300 mg daily.
- Pyrazinamide: if body weight < 50 kg, 1.5 g daily; if body weight ≥ 50, 2 g daily.
- Ethambutol: 15 mg/kg (test visual acuity before treatment).
- Give all drugs together once daily with breakfast.
- All four drugs for 2 months followed by rifampicin and isoniazid for 4 months (having checked the sensitivities).
- Tuberculous meningitis: recommended duration 12 months:
 - Four drugs for 3 months: rifampicin + isoniazid for 9 months.
 - Corticosteroids are indicated in tuberculous meningitis, pericarditis and spinal tuberculosis with neurological compression.

NB: This patient may have multi-resistant TB (MRTB).

Monitor therapy

- Liver biochemistry
- Patient compliance with medication.

Further reading

Maartens G, Wilkinson RJ. Tuberculosis. *Lancet* 2007; 2030–2243.
WHO Global tuberculosis control 2011. http://www.int/tb/publication/global_report/en/index./html

PLEURAL EFFUSION

This is an excessive accumulation of fluid in the pleural space. It can be detected on X-ray when 300 mL or more of fluid is present and clinically when 500 mL or more is present. The chest X-ray appearances range from the obliteration of the costophrenic angle to dense homogeneous shadows occupying part or all of the hemithorax. Fluid below the lung (a subpulmonary effusion) can simulate a raised hemidiaphragm. Fluid in the fissures may resemble an intrapulmonary mass.

Case history (1)

A 63-year-old man presented with a 2-month history of increasing breathlessness and could only walk at a slow pace on the level.

On examination he showed:

- Reduced chest movement on the right
- Reduced tactile vocal fremitus
- Stony dullness to percussion
- Reduced breath sounds
- Apex beat in anterior axillary line (see CXR in Fig. 11.2 on p. 335).

Extra signs to look for

- Clubbing: suggests malignancy
- Glands in neck
- Wasting
- Enlarged liver.

What do you do next?

Admit him to MAU. A diagnostic aspiration was performed after procedure was explained to the patient and consent obtained:

A syringe with a 21 G needle was used to obtain 20 mL of fluid. This was sent to the laboratory for:

- Protein/LDH
- Cell count
- Culture including TB
- Cytology for malignant cells.

Result

- Fluid is blood stained.
- Fluid protein is > 30 g/L, which indicates an exudate.
- Few white cells and mesothelial cells.
- Cultures sterile.
- Malignant cells: probably squamous origin.
 - **Diagnosis. Malignant pleural effusion.** Underlying squamous cell carcinoma of bronchus.

If the diagnosis had not been obtained on the aspirate, a pleural biopsy and a larger volume of pleural fluid with cytological examination of the spun cellular debris could have been performed.

If still no diagnosis, refer to respiratory physician.

What next?

- The patient has inoperable lung cancer (malignant cells in fluid).
- Treatment should be discussed at an MDT meeting concentrating on relieving symptoms and discussion of possible chemotherapy.

Drain the effusion (following explanation and consent) with an intercostal drain placed ideally over the top of the diaphragm.

An ultrasound to guide placement is useful. A small-bore (10–14 F) intercostal drain should be the initial choice. Clamp intermittently and limit flow to 1 L in the first hour to reduce the risk of re-expansion pulmonary oedema or discomfort from mediastinal shift. Re-expansion pulmonary oedema occurs much more commonly following re-expansion of the collapsed lung associated with a pneumothorax. It relates to endothelial dysfunction and is not therefore hydrostatic. Diuretics are not helpful and may exacerbate any tendency to hypovolaemic hypotension.

- **Progress.** This man's breathlessness improved after drainage of the effusion and he was discharged with an appointment with the Palliative Care team.

Case history (2)

A 43-year-old woman developed increasing breathlessness and malaise after being treated for pneumonia with oral cefalexin 2 weeks previously. She was febrile with a temperature of 39°C, flushed and anorexic with signs of a **left pleural effusion**. A pleural tap produced cloudy, infected fluid (an empyema). A diagram of the CXR appearances is shown in [Figure 11.11](#).

What should you do?

- Drain the fluid by placing an intercostal drain.
- Start antibiotics (after taking blood and fluid cultures). This should cover both aerobic and anaerobic organisms: cefuroxime 1 g 6-hourly IV, metronidazole 500 mg IV 8-hourly for 5 days, followed by oral cefaclor and metronidazole for 2–4 weeks.
- Consult chest physician/surgeon early if drainage is incomplete. Decortication of the lung or a rib resection and wide-bore drain might be needed.
- Bronchoscopy should be performed to exclude bronchial obstruction. CT scanning is helpful to assess presence of underlying lung abscess.

Causes

- Malignancy
- Mesothelioma
- Metastatic cancer: breast, bowel
- Lymphoma

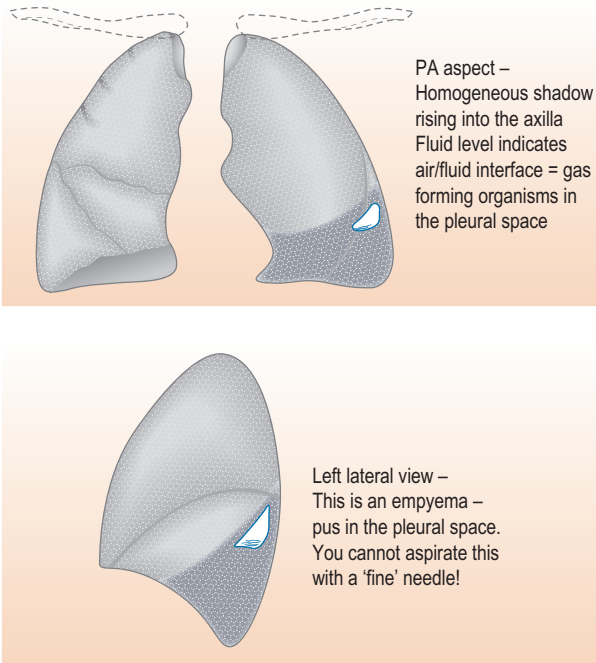


Figure 11.11 Diagram of chest X-ray (PA and left lateral) of an empyema.

- Pneumonia
- Tuberculosis
- Heart failure
- Nephrotic syndrome
- In association with intra-abdominal sepsis or pancreatitis.

Remember

If in doubt:

- Consult a more senior colleague
- Learn under supervision.

- **Progress.** This patient had an **empyema**. She was in hospital for 10 days as her recovery was slow. She required two further drainages of her empyema but surgery was not required. When seen 4 weeks later she was well.

Further reading

Davies CW, Gleeson FV, Davie RJ. Pleural Disease Group British Thoracic Society guidelines for the management of pleural infection. *Thorax* 2003; 58 (Suppl II): 18–28.

PULMONARY EMBOLISM (AND DEEP VEIN THROMBOSIS)

Pulmonary embolism is due to thrombus formed in the systemic veins (rarely the right side of the heart) which breaks off and embolises in the pulmonary artery. The clinical scenarios depend on whether the emboli block small/medium arteries or the pulmonary artery itself, causing right ventricular obstruction.

The diagnosis of pulmonary embolism can be difficult for a number of reasons:

- It is often not present when thought of
- It is present when not thought of
- Presumptive treatment is not without risk
- Proving the diagnosis may be difficult.

Case history (1)

A 24-year-old woman had been getting breathless for 3 months when referred. Asthma seemed unlikely (peak flow from referring doctor was 460 L/min) and the CXR was normal. A short pulmonary early diastolic murmur was noted and a cardiology opinion sought. Spirometry was normal but CO gas transfer was reduced (TL_{CO} 60% predicted). The echocardiographic appearances were normal.

About 2 weeks later she was admitted in shock. The ECG showed acute right heart strain (S1, Q3, T3 with dominant R waves in V1–3) and the pulmonary artery diastolic pressure with the right atrial pressure was calculated to be 25 cmH₂O (by Doppler echocardiography of the tricuspid regurgitant wave), which is very high.

- **Diagnosis.** This is a massive pulmonary embolism.

She was managed on the CCU with intravenous alteplase 10 mg IV over 1–2 min followed by IV infusion of 90 mg over 2 h and the Doppler echocardiogram used to monitor response.

She responded well to treatment and was returned to the ward.

- **Progress.** A subsequent \dot{V}/\dot{Q} scan revealed the typical multiple patchy perfusion abnormalities of recurrent minor pulmonary embolism, which explains her 3-month history of breathlessness. The scan has remained abnormal and she has continued to be breathless. Leiden factor V deficiency was discovered and the oral contraceptive stopped. She has been advised to remain on life-long warfarin.

Other common clinical scenarios caused by pulmonary embolisms you will meet are:

- Acute minor pulmonary infarction producing pleuritic chest pain and possibly haemoptysis.

- Episodic non-specific symptoms in the postoperative patient (such as palpitations and anxiety attacks) possibly followed by a cardiac arrest when at toilet.
- Chronic minor thrombo-embolism leading to established pulmonary hypertension.

Information

90% of patients with a pulmonary embolus have chest pain and/or breathlessness as the major complaint.

The source of dislodged thrombus is most commonly the pelvic or femoral veins, with the classical triad of stasis, hypercoagulopathy or trauma being present in most patients. In some circumstances air, amniotic fluid, infected clot and even sheared off intravenous catheter material may be causal.

Venous thrombosis occurs in 10% of hospitalised patients and was much more common on surgical wards before routine prophylaxis was introduced. Patients with malignancy, advanced cardiorespiratory disease or a past history of venous thrombosis are most at risk.

All medical patients expected to be in bed for more than 3 days should be given DVT prophylaxis. Risk calculation should now guide prophylaxis, which should include pressure stockings as well as heparin (low molecular weight).

- **Simple investigations.** These are usually only helpful when the diagnosis is clinically obvious.
- Plasma D-dimers are very useful and if negative rule out pulmonary embolism.
- The ECG or CXR might, however, reveal evidence of alternative causes such as myocardial infarction, pneumothorax or aortic dissection.

Information

An undetectable plasma D-dimer level (reflecting fibrin activation) essentially excludes significant thromboembolism but a raised value is non-specific.

Invasive investigations

- **CT.** Contrast-enhanced, multi-detector CT angiograms (CTAs) have a sensitivity of 83% and specificity of 96%, with a positive predictive value of 92% (higher with 64-multislice scanners).
- **Radionuclide ventilation/perfusion scanning (\dot{V}/\dot{Q} scan).** This is a good test after measurement of D-dimers. It demonstrates ventilation/perfusion defects, i.e. areas of ventilated lung with perfusion defects. Pulmonary ^{99m}Tc scintigraphy demonstrates the underperfused areas, while a scintigram, performed after inhalation of radioactive xenon, shows no ventilatory defect. A matched defect may, however, arise with a PE that causes an infarct, or with emphysematous

bullae. This test is therefore conventionally reported as a probability (low, medium or high) of PE and should be interpreted in the context of the history, examination and other investigations.

- **MRI.** This gives similar results to CT and is used if CTA is contraindicated.

The echocardiogram can be very useful in the diagnosis of massive PEs but is of limited value otherwise:

- It might show RV dilation with paradoxical septal wall movement; pulmonary artery pressure may also be estimated.
- It might exclude or confirm an alternative diagnosis, e.g. cardiac tamponade, LVF.
- RV clot is occasionally imaged and is an adverse prognostic sign with 10% mortality risk.
 - **Look for DVT.** Doppler ultrasound or B-mode venous compression ultrasonography of the legs has largely replaced contrast venography, having sensitivities of 90% and 70%, respectively, for proximal thrombus. This can detect clots in the pelvic or ilio-femoral veins.

Treatment

Supportive therapy with oxygen and analgesia should be given.

In the original trials of IV heparin in patients with obvious clinical venous thrombosis and pulmonary embolism, treatment with heparin reduced mortality from 40% to 7%:

- Low molecular weight heparin (LMWH) is licensed for use in DVT and patients with minor PE, e.g. pulmonary infarction can be treated without admission if the necessary organisation is available in the community. Use unfractionated heparin if rapid reversal is required.
- These treatments only prevent further clot formation.
- Warfarin is started and heparin discontinued once INR is therapeutic (INR 2–3).
- 6 months' warfarin is adequate therapy and 6 weeks might be sufficient in patients with surgery as the provoking factor and no underlying coagulopathy. Anti-thrombin agents, e.g. dabigatram, are being used in place of heparin and warfarin.
- Thrombolytic therapy is used for clot lysis in major pulmonary embolism. There is increasing experience of thrombolytic therapy. Although good evidence of reduced mortality is lacking, there is faster and more complete resolution of echocardiographic abnormalities or \dot{V}/\dot{Q} defects:

Information

Thrombolysis should be used in all patients with cardiogenic shock due to massive PE. You should discuss with your consultant before treating.

- Emergency embolectomy is rarely a possibility – it can be performed only in cardiothoracic centres.

- Transvenous placement of venocaval filters is used for recurrent PE even though the patient is adequately anticoagulated.

Further reading

Agnelli G. Current concepts. Acute pulmonary embolism. *N Engl J Med* 2010; **363**: 266–284.

British Thoracic Society. Guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003; **58**: 470–484. Available online: www.throaxjnl.com

PNEUMOTHORAX

Case history (1)

A 23-year-old man presented to the A&E Department with sudden onset of right-sided chest pain worse on deep inspiration associated with acute breathlessness. This started at rest and was not associated with cough. There were no pre-existing medical problems and no other symptoms.

On examination he was a healthy young man:

- Afebrile, not cyanosed, no signs of DVT
- Pulse rate 100/min; respiratory rate 30/min
- Trachea central
- Chest movement reduced right side
- Percussion note hyper-resonant right side
- Breath sounds reduced right side
- Key investigation: chest X-ray (Fig. 11.12): CXR findings pneumothorax = 1/2 hemithorax.

Key points

Common causes of pleuritic chest pain and dyspnoea are: pneumothorax, pulmonary embolism, pneumonia with pleurisy.

Diagnosis

Right-sided spontaneous pneumothorax.

Management of pneumothorax

- If < 2 cm: discharge and review next day
- If SOB \pm > 2 cm rim on CXR: aspirate
- If still unsuccessful: insert intercostal drain.

This man was symptomatic and had a moderate-sized pneumothorax. Aspiration is the first choice. Explain and obtain consent:

- Technique for simple aspiration:
 - Infiltrate with local anaesthetic down to pleura in second intercostal space in mid-clavicular line using FG16 cannula (or less) at least 3 cm long.
 - Once in pleural space, remove needle.
 - Connect cannula via three-way tap to chest, 50 mL syringe.

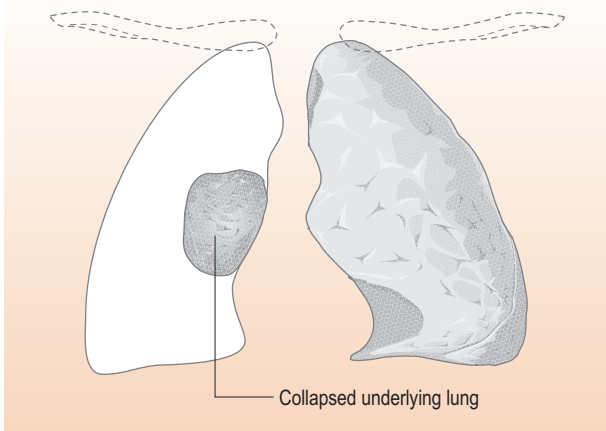


Figure 11.12 Diagram of chest X-ray showing collapsed right lung (pneumothorax).

- Stop aspirating when resistance felt, or patient coughs or complains of discomfort, or when 2.5 L aspirated.
- Patient re-X-rayed: the lung had partially re-expanded.

Further management

- Patient was discharged home after observation and some resolution on CXR, taking his discharge X-ray.
- Instructed not to fly for 6 weeks or go deep-sea diving.
- Given follow-up appointment in chest clinic for 1 week.
- Instructed to re-attend (bringing X-ray) if he became breathless.
 - **Progress.** This man's follow-up X-ray was normal and he has had no further problems.

Case history (2)

A 69-year-old man with long-standing COPD and an exercise tolerance of 100 yards on the flat became acutely breathless at rest. On examination he was distressed and cyanosed:

- Using accessory muscles of respiration
- Respiratory rate 40 per minute
- Pulse 120; BP 100/60
- Barrel-shaped chest with poor expansion
- Hyper-resonant chest with almost inaudible breath sounds.

Main differential diagnoses

- Acute exacerbation of COPD but no obvious infection and symptoms very acute

- Pulmonary embolism
- Pneumothorax
- Acute myocardial infarction with LVF.

Action

Urgent chest X-ray, arterial blood gas.

Diagnosis

Life-threatening **tension pneumothorax**: emphysematous lungs with mediastinal shift to the right and complete left pneumothorax.

Management

- Controlled oxygen as per blood gases
- Urgent insertion of cannula followed by insertion of intercostal tube.

Information

Management of intercostal tube

Insertion of tube:

- Explain and reassure patient throughout. Obtain consent
- Premedicate with opiate and atropine to prevent reflex bradycardia, particularly if patient anxious, in patients with pre-existing lung disease
- Double-check the site of pneumothorax
- Site: 4–6th intercostal space in anterior axillary line – mark with pen + position patient supine with head at 30° and arm abducted to 90°
- Wear sterile gloves
- Drain 10–14 FG (adult). Check assembly and tight connection and that underwater seal is ready
- Local anaesthetic:
 - Intradermal bleb in appropriate intercostal space
 - Infiltrate deeper with blue, then green needle to parietal pleura at upper surface of rib: NB neuro-vascular bundle runs along lower surface
 - Use 5 to 10 mL 1% lidocaine
 - Check intermittently if in pleural space (air aspirated into syringe).

Insertion of drain:

- 1 to 2 cm incision in skin and subcutaneous fat
- Insert two horizontal sutures across incision (leave loose for subsequent sealing of wound on drain site)
- Wide tract made through intercostal muscles down to and through pleura by blunt dissection with forceps (not sharp trocar)
- Insert tube using Seldinger technique and drain assembly without force
- Withdraw metal needle 5 cm and advance tube in apical direction
- Remove metal needle and connect tube to underwater seal

Continued

Information (continued)

- Secure tube firmly with one or two sutures (1 loop through skin and 4 times round tube). Purse string suturing is no longer advised as it leaves unsightly scarring
- Loop tube and secure to skin with plaster (*Note*: no kinks)
- Prescribe adequate oral/IM analgesia.

Removal of tube:

- Leave tube draining until no further bubbling + then re-X-ray (X-ray earlier if in doubt about site or efficacy of tube). *Note*: if level not swinging tube blocked. Clear or replace if lung not re-expanded
- Some patients need premedication for tube removal
- Remove holding suture and withdraw while patient breath-holds in expiration
- Seal wound with one of original sutures
- Observe overnight and if no recurrence of pneumothorax (clinical and X-ray) discharge with Chest Clinic appointment in 7 to 10 days. Patient keeps last X-ray to bring to appointment or to A&E in emergency.

- **Progress.** A chest X-ray at the Chest Clinic at 10 days showed full expansion of the lungs. He was asymptomatic but apprehensive about having a recurrence. He was reassured that this was unlikely.

Further reading

Henry M, Arnold T, Harvey J. Pleural Diseases Group. British Thoracic Society guidelines for the management of spontaneous pneumothorax. *Thorax* 2003; **58** (Suppl II): ii39–ii52.

CARCINOMA OF THE BRONCHUS

Case history

A 53-year-old male presents with a history of having coughed up blood a few hours ago. He has been smoking 20 cigarettes a day for the past 30 years. On examination there are diminished breath sounds at the right upper chest anteriorly.

What is the most likely diagnosis and why?**Carcinoma of the bronchus:**

- Cigarette smoking is the most common risk factor
- It is a common cause of haemoptysis in smokers > 40 years of age
- Physical sign of diminished breath sounds suggests bronchial obstruction.

Information

Carcinoma of the bronchus:

- Most common form of cancer in both sexes
- Non-small cell:
 - Squamous cell carcinoma (39%)
 - Large cell carcinoma (25%)
 - Adenocarcinoma (10%)
 - Alveolar cell carcinoma (2%)
- Small cell (20–30%)

What are the diagnostic investigations?

- Chest X-ray
- Sputum cytology
- Bronchoscopy for histological diagnosis
- CT.

If histological diagnosis is not made on bronchoscopy, CT-guided percutaneous needle biopsy should be performed.

Radiological manifestations of lung cancer

Screening for lung cancer has been shown to be ineffective in reducing the mortality rate. Chest X-ray is the first diagnostic investigation for lung cancer. Evidence on chest X-ray depends on:

- Location of tumour
- Its effect on neighbouring tissues:
 - Central lung shadow: about 70% of cancers, mostly small cell and squamous cell, arise centrally and present as a shadow in the hilar region and/or in the mediastinum due to involvement of lymph nodes (Fig. 11.13).
 - Peripheral lung shadow: some tumours, especially adenocarcinoma, appear as a rounded shadow in the periphery.
 - Collapse of lung parenchyma: centrally located tumours often result in collapse of a lobe by obstruction of the bronchus (Figs 11.14 and 11.15).
 - Collapsed whole left lung (Fig 11.16). NB: Collapse of whole lung is also seen postoperatively due to retained sputum.
 - Pleural effusion: a large pleural effusion is almost always due to invasion of pleura by malignant cells and its presence is a contraindication for surgical resection. A small pleural effusion might occur without invasion of malignant cells and hence surgical resection may still be considered.
 - Rib erosion: the classic presentation is erosion of the first rib seen with an apical neoplasm (Pancoast tumour) often associated with Horner's syndrome. Rib erosion itself is not a contraindication for surgical resection.

Other presentations are:

- Cachexia or metastatic disease
- Raised hemi-diaphragm due to phrenic nerve palsy.

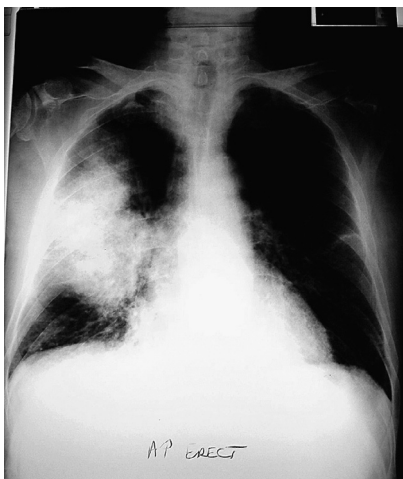


Figure 11.13 Chest X-ray showing a shadow in the right mid-zone (note the area of consolidation with irregular margins).

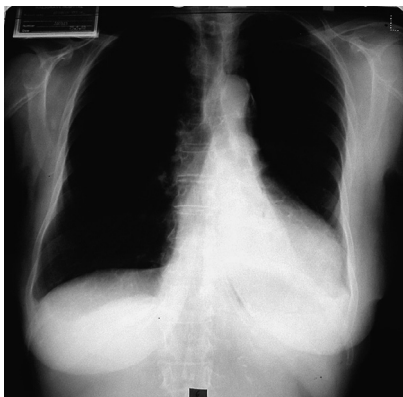


Figure 11.14 Chest X-ray showing a left lower lobe collapse.

Differential diagnosis

Pneumonia

The possibility of lung cancer should be considered in a smoker with shadow on chest X-ray diagnosed as due to pneumonia:

- Presence of lobar collapse on chest X-ray
- Irregular margins of the lung shadow representing consolidation
- Absence of constitutional symptoms associated with pneumonia
- Symptoms such as haemoptysis and weight loss prior to the development of pneumonia, especially in middle-aged or elderly smoker.

Patient should be investigated for lung cancer if:

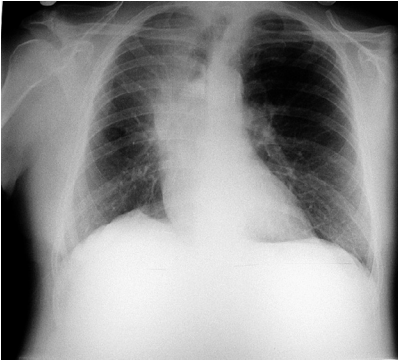
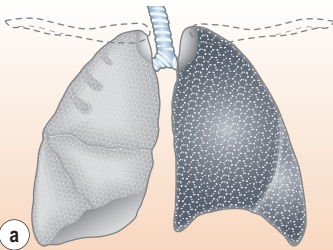


Figure 11.15 X-ray showing right upper lobe collapse.



- Homogeneous opacification of left hemithorax
- Trachea deviated to the left
- Mediastinal shift
- Left heart border obscured
- Left diaphragm raised

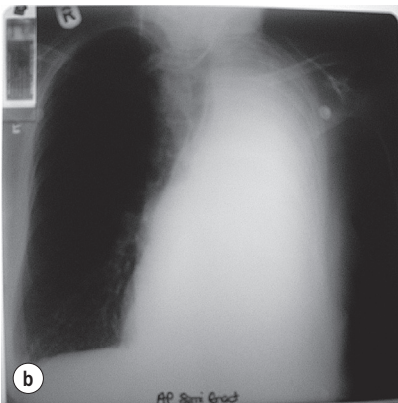


Figure 11.16 Diagram (a) and chest X-ray (b) showing a complete collapse of the left lung. Note that the mediastinum has been shifted to the left.

- Patient does not respond to treatment, especially if there are risk factors such as smoking and the susceptible age group.
- Satisfactory radiological resolution has not occurred 6 weeks following treatment for pneumonia resulting in clinical response.

Tuberculosis

- Tuberculosis is more often seen in young age group.
- Constitutional symptoms such as low-grade pyrexia and night sweats are often present in tuberculosis.
- Cavitation is uncommon in lung cancer but may occur in squamous cell type. The wall of the cavity is thick and irregular in lung cancer.

Management

For practical purposes carcinoma of the bronchus can be divided into:

- Small-cell lung cancer (SCLC): this is rarely operable.
- Non-small cell lung cancer (NSCLC).

Information

SCLC

- Limited disease: tumour confined to one hemithorax and ipsilateral supraclavicular node
- Extensive disease: involvement of any site outside the hemithorax

What treatments can be offered to a patient?

All patients should be referred to a multidisciplinary team (MDT) for discussion of management, which is then discussed fully with the patient before decisions are made.

Small-cell lung cancer

- **Prognostic factors** The staging of small-cell lung cancer is divided into limited and extensive disease (see above). Systemic therapy is the primary therapeutic modality because of the usually disseminated nature of the disease.
- **Treatment** *Limited disease* is present in approximately 30% of patients and is best treated with concurrent chemo- and radiotherapy using a combination of cisplatin and etoposide or irinotecan, which increases the survival at 5 years from 15% to 25% compared with radiotherapy alone. A similar degree of improvement can also be achieved with hyperfractionated radiotherapy. Prophylactic whole-brain radiation to prevent cerebral metastases can reduce symptomatic CNS disease and improve overall survival by 5%.

Extensive disease can be palliated with the combination of carboplatin and etoposide or irinotecan, which when compared with best supportive care can increase median survival from 6 months to 9–13 months and 2-year survival to 20%.

- Severe pain: potent analgesics, e.g. opiates, including fentanyl.
- Bone pain:
 - NSAIDs
 - Local radiotherapy.

- Nerve root pain:
 - Amitriptyline
 - Carbamazepine.

Management of major complications

Hypercalcaemia (see p. 447)

- Intravenous fluids: 3–4 L
- Diuretic: furosemide 40 mg IV (ensure adequately rehydrated)
- Intravenous pamidronate: treatment of choice.

Weakness of legs

This suggests spinal cord compression and is a medical emergency especially with bladder or bowel dysfunction:

- Start dexamethasone 4 mg \times 3 daily
- MRI scan of the spine and referral for radiotherapy/surgery.

Stridor

This is due to obstruction above the level of carina (demonstrated in a flow volume loop):

- Start dexamethasone 4 mg \times 3 daily
- Urgent bronchoscopy followed by CT scan of the chest/neck
- Intraluminal growth: referral for laser therapy/stenting
- Extrinsic compression: referral for radiotherapy/stenting.

Superior venacaval obstruction

- Start on dexamethasone 4 mg \times 3 daily.
- Refer for radiotherapy.
- Consider heparin or thrombolysis.

Management of patients with neutropenia following chemotherapy

Investigations

- Blood (preferably two samples from two different sites) and urine cultures
- Chest X-ray
- Culture from any suspected site of infection, e.g. cannula exit site, sputum

Indications for antibiotic therapy

- Absolute neutrophil count $<$ 1.0/total white cell count $<$ 2.5
- Pyrexia.

Recommended antibiotic regimens

- IV gentamicin 3–5 mg/kg IV once a day (monitor trough levels) and a ureidopenicillin (Piperacillin with Tazobactam 4.5 g every 6 hours).
- In presence of severe renal insufficiency, replace gentamicin with IV ceftazidime 1–2 g \times 3 daily or ciprofloxacin 400 mg \times 2 daily.
- Continue antibiotics for 5 days or until white cell counts are in normal range and symptoms have remitted.

If no improvement after 48 to 72 h of antibiotic therapy

- Repeat blood and urine cultures and chest X-ray
- Consider the following infections:
 - Fungus: blood and urine cultures
 - Start fluconazole and/or amphotericin
- Protozoa: broncho-alveolar lavage
- Virus: viral serology
- Resistant staphylococcus:
 - More common with central venous catheter
 - Treat with vancomycin.

Indications for Filgrastim (G-CSF) – specialist use only

- Absolute neutrophil count: 0.2
- Persistent neutropenia (< 1.0 for more than 48 h)
- Stop therapy when absolute neutrophil count is 1.5 or more.
 - *Progress.* This man was found to have non-small cell carcinoma of the bronchus-squamous cell type. The MDT consensus was that surgery was not an option. He was given radiotherapy followed by chemotherapy. Follow-up at 6 months showed deterioration of his condition and he was referred to the palliative care team.

Further reading

Goldstraw P, Ball D, Jett JR et al. Non-small-cell lung cancer. *Lancet* 2011; **378**: 1727–1740.

Van Meerbeeck JP, Fennell DA, De Ruyscher DK. Small-cell lung cancer. *Lancet* 2011; **378**: 1741–1755.

Websites for guidelines on lung cancer

British Thoracic Society Guidelines: www.brit-thoracic.org.uk

Royal College of Radiologists: Guidelines on the Non-Surgical Management of Lung Cancer: www.rcr.ac.uk/oncologytemplate

SARCOIDOSIS

Sarcoidosis is a multi-system granulomatous disorder of unknown aetiology. It commonly presents with bilateral lymphadenopathy, pulmonary infiltration and skin and eye lesions.

Case history (1)

You are phoned up by a primary care physician who has a 28-year-old woman with tender, bluish lumps on the front of her legs in the clinic. She also complains of stiffness of the ankles and a temperature. The doctor thinks that this is erythema nodosum but would like another opinion.

Is this erythema nodosum (EN)?

From the description this sounds very likely and you ask the doctor to send the patient up to outpatients when you will arrange for a CXR to be performed (Fig. 11.17).

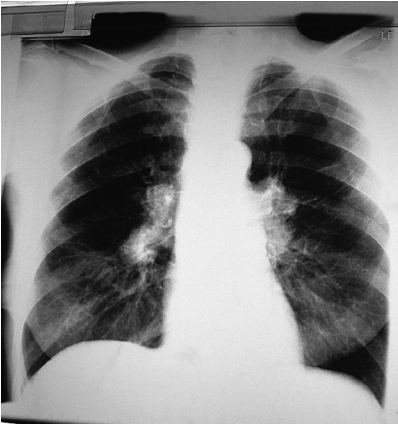


Figure 11.17 Bilateral hilar lymph node enlargement – sarcoidosis.

EN with lymphadenopathy on CXR is a characteristic presentation of **sarcoidosis**. Along with her arthritis and fever, the syndrome is called Löfgren's syndrome. In outpatients, the patient poses several questions for you on hearing her diagnosis.

What is sarcoidosis?

You explain that this is a well-recognised disorder for which no cause is known. You emphasise, however, that in her case the skin rash (EN) will subside within 2 months but the CXR might take up to a year to revert to normal. No treatment is required other than pain relief.

The chances of further trouble are negligible.

You discuss this later with your consultant, who reminds you of the extrapulmonary manifestations that can be troublesome (**skin and ocular lesions** are most common):

- **Skin lesions:** 10% of cases. Apart from EN, a chilblain-like lesion (lupus pernio) and nodules are seen.
- **Eye involvement:** 5% of cases. Anterior uveitis (misting of vision, pain, red eye) is common. Posterior uveitis may present with a progressive loss of vision. Conjunctivitis and retinal lesions are seen. Asymptomatic uveitis may be found in 25% of patients.
- **Metabolic hypercalcaemia:** found in 10% but it is rarely severe.
- **CNS involvement:** is rare (2%) but can lead to severe neurological disease.
- **Bone and joint involvement:** arthralgia without EN is seen in 5% of cases.
- **Cardiac involvement:** is rare (3%) clinically, although seen in 20% of post-mortems. Ventricular arrhythmias, conduction defects and cardiomyopathy with CCF are seen. The serum ACE is insensitive in cardiac sarcoid and echocardiography should be performed in chronic sarcoidosis.

Your consultant does say that the above list is comprehensive but fortunately the conditions are rare.

- **Progress.** The patient made a good recovery and her EN settled after 2 weeks. A follow-up chest X-ray at 6 months was normal.

Case history (2)

You are contacted by the ENT registrar because he has seen a 48-year-old patient with nasal stuffiness and a blocked nose. He had also noted some blood-stained nasal discharge. An X-ray of the patient's sinuses shows destruction of the nasal bones. He wants you to see the patient because he found out that this man has had long-standing **pulmonary sarcoidosis**. As you walk to the ENT ward you go over your knowledge of sarcoidosis, remembering that patients with upper respiratory tract involvement usually have pulmonary disease.

On arrival on the wards you retake the history – he has been breathless for years and tells you that all his numerous CXRs show that his lungs are 'full of sarcoid'. He has not been on steroids because of their lack of efficacy and side effects, which have made him non-compliant.

On examination he is noticeably breathless and cyanosed. Chest examination shows widespread crackles.

You arrange to give the patient oxygen by ordinary face-mask 4 L/min.

Investigations

- CXR
- FBC shows:
 - A mild normochromic normocytic anaemia
 - Low lymphocyte count \pm low neutrophils
 - Thrombocytopenia
- Blood gases PO_2 6.8 kPa, pCO_2 4.3 kPa

The next morning you return with your consultant, having obtained the patient's old notes.

You note multiple CXRs showing widespread pulmonary infiltration with no hilar lymphadenopathy. The latest CXR also shows a rounded opacity in the right apex – thought to be an aspergilloma.

Fibre optic bronchoscopy with transbronchial biopsies was performed 10 years ago. This showed epithelial and giant cell granulomas (this test has a 90% sensitivity with pulmonary infiltration).

Lung function tests showed:

- Reduced total lung capacity (restrictive ventilatory capacity)
- Impaired gas transfer (TLCO)
- Low compliance
- Serum ACE level: this had been done a few years back and was found to be raised.

Review of his past treatment shows that he has been given steroids on many occasions and azathioprine and methotrexate as steroid-sparing agents.

Your consultant congratulates you on your review of the notes, which is crucial for the future management of this case. In a patient with such severe disease, he suggests you start high-dose steroids and then a trial of azathioprine and infliximab for which there is some evidence of efficiency.

Progressive respiratory failure is well recognised in sarcoidosis. Unfortunately, recurrence in the transplanted lung (as well as limited availability of organs) has led many centres to not consider transplantation for end-stage pulmonary fibrosis. Lung transplantation may be indicated if this patient fails to improve.

Remember

- Persistently raised levels are a poor guide to clinical activity.
-
- **Progress.** This man's chest condition remained static, despite a further trial of steroids and azathioprine. He continues to be breathless but is, for the moment, coping. He has been referred to the transplant team for assessment in view of his young age.

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SHOCK

Case history (1)

A 60-year-old bank manager presents with crushing central chest pain. This started 45 minutes ago and has remained constant ever since.

On examination he is pale and clammy. His pulse is 100/min, poor volume and BP 90/60.

- **Diagnosis.** Shock – cardiogenic; ECG shows evidence of anterior myocardial infarction.

Case history (2)

A 50-year-old man who works in a bar has been brought to hospital vomiting a large amount of blood. He gave no history of upper abdominal pain but did admit to drinking a bottle of whiskey a day and occasional beers as well.

He also admits to a previous hospital admission with abdominal swelling which was due to alcoholic liver disease. He was told that his liver disease was bad and that he must stop drinking and take propranolol regularly as he had varices on endoscopy. He had not stopped drinking, nor was he taking his propranolol.

On examination he is sweating profusely with visible shaking of his extremities. His pulse rate is 120/min with a blood pressure of 90/60.

- **Diagnosis.** Shock – hypovolaemia due to blood loss, probably from oesophageal varices.

Remember

- Shock is a life-threatening condition in which the patient is suffering global hypoxic injury
- Establish clear airway
- Oxygen must be given immediately to all haemodynamically unstable patients.

Physiology (Fig. 12.1)

Shock is 'inadequate tissue oxygenation' where there is failure of the circulatory system due to:

- Failure of the heart to maintain an adequate cardiac output, e.g. myocardial infarction
- Reduction in the volume of blood within the circulation, e.g. haemorrhage
- Loss of vascular tone within the circulatory system, e.g. septicaemia
- Obstruction to the circulation, e.g. pulmonary embolism.

Causes of shock

- Cardiogenic: myocardial infarction, tamponade, aortic dissection, pulmonary embolism

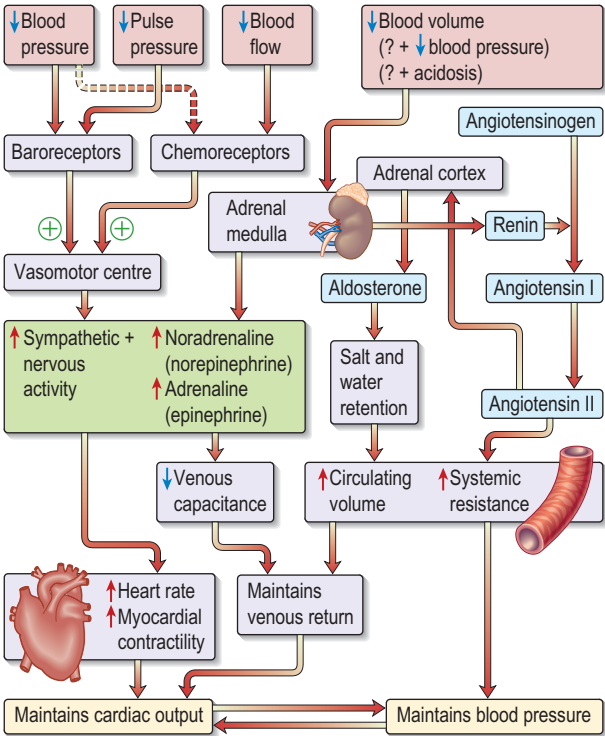


Figure 12.1 The sympatho-adrenal response to shock showing the effect of increased catecholamines on the left of the diagram and the release of angiotensin and aldosterone on the right. Both mechanisms result in maintaining the blood pressure and cardiac output in shock.

- Sepsis: infective causes, e.g. pneumonia, urinary tract infection or meningococcal septicaemia or 'systemic inflammation', resulting from trauma, post-surgery or anaphylaxis
- Hypovolaemia: profound dehydration, haemorrhage.

Remember

A patient might have more than one cause of shock, e.g. Case 2 may have an alcoholic cardiomyopathy (pump failure) as well as his haematemesis (decreased blood volume).

Is the shock state in Case 1 due to myocardial infarction, an obstructed circulation or other shock-inducing factors?

A history in a shocked patient of chest pain associated with ECG evidence of a **myocardial infarction** makes the diagnosis in this case. However, be careful because ECG changes with tachyarrhythmias and some ST segment changes which look characteristic of myocardial ischaemia can also occur in other types of shock.

Is the shock state in Case 2 due to fluid loss? If so, what fluid and from where?

In this case the blood loss is obvious, i.e. haematemesis. Try and estimate from the patient how much was lost. In other cases blood loss might be concealed, e.g. pancreatitis.

Clinical examination

In assessing the shocked patient the following indices should be monitored:

- Pulse rate and respiratory rate
- Peripheral venous filling/capillary filling
- Limb temperature
- Arterial blood pressure
- Urinary output
- Mental status.

Investigations

- Haemoglobin and haematocrit, U&Es, LFTs, troponin estimation
- ECG and monitor
- Central venous pressure (see p. 225)
 - If the CVP is low (< 5 mmHg) fluid replacement is necessary
 - If 10 mmHg or more, fluid replacement is probably not required immediately

Case 1 – has a problem with the circulatory pump and probably needs no extra intravascular fluid administration.

Case 2 – the haematemesis patient – has lost circulating volume with a low central venous pressure. His problems are with the plumbing circuit

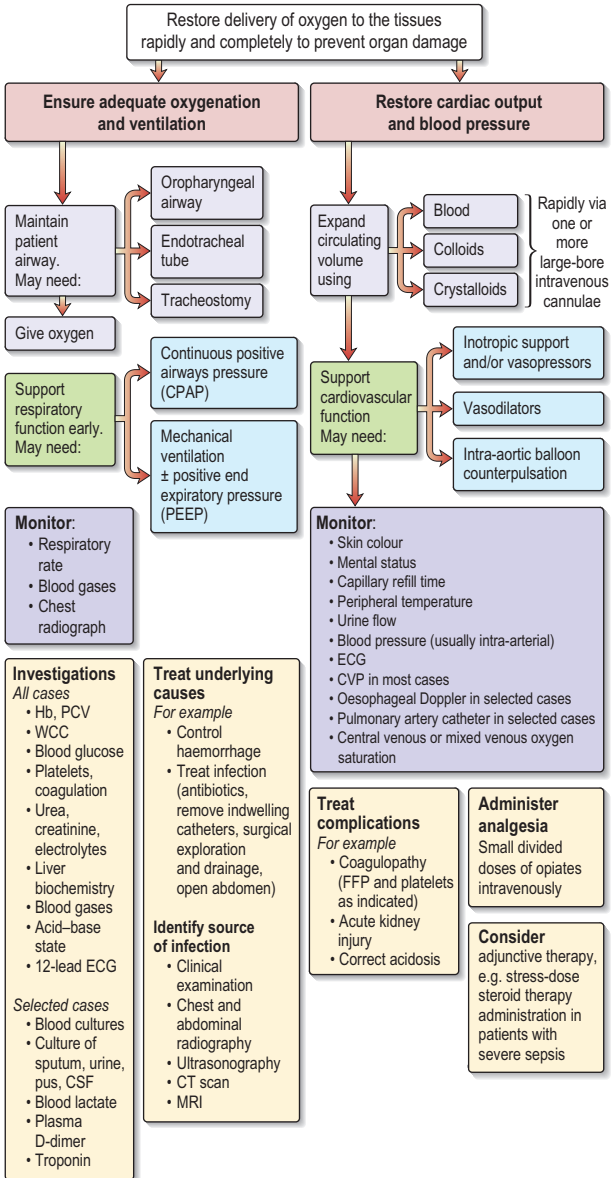


Figure 12.2 Management of shock. Patients require intensive nursing care.

not the heart pump but his condition might be compounded by coagulation and biochemical disturbances consequent upon hepatic insufficiency.

Other investigations (see Fig 12.2)

- Arterial blood gas analysis: in hypovolaemic shock (as in all shock states) there is a metabolic acidosis with a high hydrogen ion concentration and low bicarbonate concentration. In cases with respiratory complications the pO_2 and pCO_2 values will help indicate the need for ventilatory support.
- Lactate levels: blood lactate levels rise approximately in proportion to the severity of the shock.
- X-rays: these are usually of little value in the acute stages of shock management. A CXR will exclude any treatable pathology, such as a pneumothorax or haemothorax often complicating insertion of monitoring lines. A CT scan may be helpful in, for example, a case of trauma.

How would you treat?

Both patients should be admitted to high-dependency nursing units in the first instance as their MEWS scores were > 5 .

Case 1

In cardiogenic hypotension key issues are pain relief, arrhythmia management and treatment of pulmonary oedema. Pain relief by incremental doses of intravenous opiates will aid reduction in myocardial oxygen consumption. Correcting electrolyte disturbances, hypoxia and controlling angina pain might assist in arrhythmia management. Temporary transvenous pacing might be required for significant bradycardia. Continuous infusion of vasodilators (e.g. glyceryl trinitrate 10–200 $\mu\text{g}/\text{min}$) plus diuretics (e.g. furosemide 40 mg) is needed for pulmonary oedema. Acute revascularisation (thrombolysis, angioplasty) might also be indicated. In the context of persistent hypotension, infusion of inotropic agents such as dobutamine (e.g. 2.5–10 $\mu\text{g}/\text{kg}/\text{min}$) might be necessary whilst correctable abnormalities are sought (e.g. acute mitral regurgitation following papillary muscle rupture or the development of an ischaemic ventricular septal defect). Percutaneous insertion of an intra-aortic balloon counterpulsation pump may be necessary for refractory cardiogenic hypotension following transfer to a specialist centre as a prelude to surgical intervention.

- **Progress.** This man initially improved on ionotropes, diuretics and vasodilatory therapy. However, he remained hypotensive, BP < 90 with poor output. He was transferred to the Cardiac Centre for insertion of an intra-aortic balloon pump. He did not respond and died 3 days later (mortality is 79% for cardiogenic shock).

Information

Patients at risk of further deterioration will have one or more of the following vital signs, which would indicate transfer to an intensive therapy unit (ITU):

- Heart rate > 120 bpm
- Heart rate < 40 bpm

Continued

Information (continued)

- Systolic blood pressure > 200 mmHg
- Systolic blood pressure < 80 mmHg
- Respiratory rate > 30 breaths per minute
- Respiratory rate < 8 breaths per minute
- Oxygen saturation < 90%
- Glasgow coma scale < 8
- Core temperature > 39°C
- Core temperature < 35°C
- Urine output less than 0.5 mL/kg/h for 2 consecutive hours.

Case 2

In hypovolaemic hypotension the principal issues are the reduction in further fluid loss and simultaneously restoring fluid volumes via wide-bore intravenous cannulae. Infusion of red cells provides sufficient oxygen transport capacity (a target of 7–9 g/dL is broadly accepted). Fresh frozen plasma (e.g. to obtain a target INR of < 1.5) might be necessary. At the earliest opportunity the patient with haematemesis will require endoscopy to find the bleeding lesion and treat (see p. 67).

- **Progress.** This man was successfully resuscitated and variceal banding was performed at endoscopy. He left hospital after 7 days and was referred to the local Liver Unit for consideration of liver transplantation (Child's Grade C alcoholic liver disease). He did not attend the clinic and was readmitted 6 weeks later in hepatic coma and died.

Case history (3)

A 68-year-old man is brought to A&E by ambulance. His wife says that he developed abdominal pain 4 days ago which has got progressively worse. He has always suffered from indigestion and pain in the stomach area after food, for which he has taken antacids with some relief.

On this occasion the pains got worse and she said her husband had refused to get out of bed and appeared to be confused and disorientated. She had called an ambulance, which brought him to hospital.

On examination he was pyrexial at 39°C. He was pale and unsure of his surroundings and moaning about his abdominal pain. His pulse was 120 beats/min with a blood pressure of 90/40 and he had a cold nose. He was breathless and his O₂ sats were 90%.

Abdominal examination revealed a distended abdomen, tender to touch, with absent bowel sounds.

What is the cause of shock in this patient?

The patient has septic shock, probably secondary to intra-abdominal sepsis. He will need fluid resuscitation and urgent investigations and probably a laparotomy.

How would you manage this case? (see Fig. 12.2)

Immediate action

- A B C D E.
- Correct hypoxaemia: high-flow O₂ via a face mask.
- Determine cause: examination, chest and abdominal X-ray, ECG, ABGs, FBC, U&Es, amylase, blood cultures.
- IV access.
- Initiate treatment: IV fluid resuscitation with 0.9% saline, inotropes if no response to fluid resuscitation.
- Insert a urinary catheter and monitor urinary output.

Shock is a medical emergency. The longer it persists, the lower the chance of recovery because secondary injury, from coexistent hypoxaemia and delayed reperfusion, is now recognised to cause further cytokine activation and the development of multiple organ failure (MOF).

Information

The medical records of many patients admitted to the ICU from the ward show progressive evidence of impending collapse – increasing heart rate, oliguria, tachypnoea or confusion.

Act before shock has become established!

Pathophysiology of septic shock

In sepsis, hypotension primarily results from impaired vascular tone. Sympathetic activation often leads to a high cardiac output with a low systemic vascular resistance. Hypovolaemia can occur from interstitial fluid losses due to widespread endothelial dysfunction and reduced venous tone. In more profound sepsis, myocardial depression also occurs due to circulating cytokines such as tumour necrosis factor (TNF).

Further management

- Early antibiotic therapy, e.g. Piperacillin with Tazobactam, as it was felt to be an upper GI perforation.
- Attempted early control of the source of infection: seek surgical opinion for treatment of abdominal condition.
- Central line for CVP measurement.
- Titrate fluid resuscitation to provide adequate cardiac output with good urine output.
- Inotropic support: give dopexamine, a dopamine analogue which is useful in patients with septic shock, as in this man with a low cardiac output and peripheral vasoconstriction.
- CPAP or intubation and IPPV.
- Early recourse to stress-dose steroid therapy if requiring vasoconstrictor therapy.
- Control blood sugar with insulin.

Summary

Timely intervention in patients with sepsis might prevent the progression of shock. Fluid resuscitation and treatment aimed at the primary cause

should be instituted rapidly and high-flow oxygen given to limit regional hypoxaemia. Prognosis is dependent on cause and response to treatment. For instance, mortality from urinary sepsis has a better prognosis than a similar clinical situation resulting from peritonitis.

- **Progress.** This man had peritonitis secondary to a perforated ulcer. He was resuscitated and admitted to the ITU. He later had a laparotomy (a laparoscopic surgeon was unavailable) with washout of the peritoneum and oversewing of the ulcer, with an omental patch. He remained in ITU, needing inotropic support and ventilation for 4 days and was then transferred to the ward. He eventually made a good recovery. *Helicobacter pylori* eradication was given.

ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Case history

You are called urgently to the emergency department when on take. A 35-year-old known drug user has been sent urgently to the hospital having been found unconscious. The Glasgow Coma Score (GCS) is 5, BP 100/60 with a respiratory rate of 20 and SaO₂ on high-flow O₂ therapy is 85%.

What are the possible causes of depressed consciousness and what are your immediate actions?

- You need to consider intoxication, hypoglycaemia, respiratory failure, head injury or a post-ictal state.
- On examination*, look for evidence of focal neurological signs, pinpoint pupils, trauma to the head or evidence of seizures such as tongue laceration, incontinence.
- Ensure airway not obstructed, establish IV access, take blood gases, blood glucose and blood and urine for toxicology.
 - ABG analysis reveals pH 7.2, PaO₂ 6.4, PaCO₂ 2.5, lactate 4.1 mmol/L.

What do these results indicate?

- Acute type 1 respiratory failure with a metabolic (lactic) acidosis.
- There is vomitus around the mouth and on his clothing. The chest X-ray shows patchy shadowing at the right base.
- Following naloxone administration he becomes agitated, moving all limbs, but does not respond purposely to command.

What is the immediate management?

Respiratory failure is probably related to aspiration of vomitus. Intubation and IPPV are indicated. CPAP or non-invasive ventilation are contraindicated because of danger of further vomiting and lack of cooperation.

He was transferred to the ICU. On the post-take ward round next morning, ventilatory pressures are high for standard tidal volumes and he remains hypoxic on F_iO₂ 100%. Your consultant suggests you make a short

presentation on acute respiratory distress syndrome (ARDS) to the students at the lunch-time meeting.

Key features of acute lung injury/ARDS

See [Figure 12.3](#):

- Pulmonary infiltrates: due to an increase in lung interstitial fluid not related to heart failure; by definition pulmonary artery occlusion pressure < 18 mmHg.
- A reduction in pulmonary compliance: i.e. stiff lungs, resulting in high inflation pressures.
- Profound gas exchange abnormalities defined as $\text{PaO}_2 : \text{FiO}_2$ ratio < 300 mmHg for acute lung injury (ALI) or < 200 mmHg for ARDS.

Causes

- Severe sepsis, e.g. peritonitis, septicaemia
- Pulmonary aspiration (as in this case)
- Multiple trauma and massive transfusion
- Post-cardiac bypass syndrome
- Pancreatitis
- Toxic fume exposure including smoke inhalation
- Cerebral injury, e.g. subarachnoid haemorrhage.

Pathophysiology

Profound hypoxaemia results from venous admixture or shunting of deoxygenated blood through poorly or unventilated lung units. This arises because:

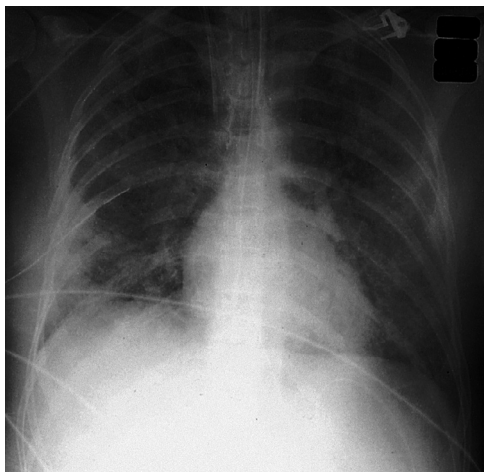


Figure 12.3 Chest radiograph appearances in adult respiratory distress syndrome (ARDS). Bilateral diffuse alveolar shadowing with air bronchograms and no cardiac enlargement. From Kumar and Clark *Clinical Medicine* 8th edn, 2012.

- Endothelial dysfunction leads to widespread interstitial oedema and impaired alveolar capillary perfusion.
- The stiff (low-compliance) lungs result in reduced tidal volume and reduced end expiratory lung volume – this then causes small airway collapse. Once collapsed, Laplace's law explains why it is difficult to re-expand the airway (consider the difficulty in initially blowing up a balloon).
- Additional small airway pathology, particularly with direct lung injury, e.g. smoke inhalation.
- The lung can be likened to a wet sponge – the dependent sponge is waterlogged and the air spaces collapsed. Only the non-dependent areas of the lung might be contributing to gas exchange. The additional component of airway inflammation in some causes of ARDS explains the high mortality associated with direct lung injury (> 60%).

Management

The high mortality of ARDS is critically dependent on resolution of the primary cause. Treatment of the lung is essentially supportive. Avoidance of further injury by tolerating relative hypoxaemia (aiming to limit oxygen toxicity by $F_iO_2 < 70\%$) and allowing permissive hypercapnia (limiting tidal volume to avoid barotrauma – overdistension of functioning lung and risk of pneumothorax). Ventilatory techniques include:

- Deep sedation and neuromuscular paralysis to increase chest wall compliance. A semi-recumbent bed position unless contraindicated.
- Small tidal volumes (6 mL/kg of predicted body weight) and prolonged inspiratory time to limit airway pressure.
- Use of a minimum amount of PEEP (positive end-expiratory pressure) to recruit lung units.
- Prone positioning to improve $\{V\dot{d}\}/\{Q\dot{d}\}$ matching and clearance of lung secretions.

Experimental methods include:

- Inhaled nitric oxide to overcome hypoxic pulmonary vasoconstriction and improve $\{V\dot{d}\}/\{Q\dot{d}\}$ matching and reduce pulmonary hypertension.
- Rescue therapy with steroids to limit the proliferative fibrotic process of lung repair.
- High-frequency ventilation.
- Extra corporeal membrane oxygenation.

Outlook

Mortality from ALI/ARDS remains high (overall 30–40%). Lung remodelling might, however, result in considerable eventual recovery. Progress of the underlying disease, hospital-acquired infection or the development of cardiogenic shock secondary to right ventricular failure are critical in determining survival.

- **Progress.** The patient developed multi-organ failure with impaired hepatic synthesis including coagulopathy, cholestatic jaundice and acute tubular necrosis requiring haemofiltration. Antibiotic therapy initially was IV cefuroxime infusion 1.5 g 6-hourly and metronidazole 500 mg IV 8-hourly, but subsequently *Pseudomonas* was cultured from respiratory secretions and IV piperacillin was started. A week later a tracheostomy was performed and ventilatory support was

progressively weaned over the next 3 weeks. He was discharged from hospital 6 weeks after admission.

Further reading

Herridge MS, Tansey CM, Matte A et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293–1304.

Patekh D, Dancer RC, Thickett DR. Acute lung injury. *Clin Med* 2011; **11**: 615–618.

Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome. *Lancet* 2007; **369**: 1556–1565.

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SELF-POISONING

This is a common problem, leading to over 100 000 hospital admissions in England and Wales per annum. It is also a problem in developing countries: in cities, drugs, e.g. diazepam, are used, while in rural areas substances such as copper sulphate and yellow oleander are often taken.

General points

- 80% of patients seen in A&E will be conscious.
- There is poor correlation between history of amount, type and timing of poisons consumed and blood toxicology.
- Frequently, more than one drug will have been consumed.
- Alcohol is the most commonly consumed second agent.
- Carefully assess suicide risk, be sympathetic and admit to MAU.

What particular points do you need to assess on physical examination?

- Assess and record conscious level using the Glasgow Coma Scale (p. 492).
- Document respiratory rate and cyanosis (use pulse oximetry).
- Measure blood pressure and pulse.
- Record pupillary size (small with opiates) and reactivity to light.
- Measure temperature: rectally if unconscious.
- If depressed consciousness, check for coexistent head injury.
- Look for needle tracks or signs of drug use.

Case history (1)

A 25-year-old woman is admitted semi-conscious, smelling of alcohol, having taken an indeterminate amount of an unknown drug at some point earlier that evening.

On examination she has depressed consciousness (GCS = 11), respiratory rate of 12 per minute, blood pressure of 95/70 mmHg and small reactive pupils.

What should you do?

- Baseline: full blood count, urea and electrolytes, liver function.
- Paracetamol and salicylate levels at 4 h or thereafter post-overdose.
- Blood and urine samples for toxicology: particularly useful in seriously ill with altered consciousness.
- O₂ saturation, arterial blood gases if depressed respiration.
- Admit patient to MAU.

Information

Self-poisoning

Take advice from the 24-h National Poisons Information Service (see end of chapter) in all serious overdoses: there might have been recent advances in management of the specific poisoning under your care.

Some common drugs used for overdose exhibit delayed action, e.g. aspirin, paracetamol, tricyclic anti-depressants, iron (more common in children), co-phenotrope, paraquat and all modified-release preparations.

General management

- Nurse in left lateral position.
- Clear mouth of vomitus, debris, obstructing objects.
- Catheterisation of bladder is usually unnecessary as gentle suprapubic pressure can empty bladder.
- IV cannula.
- Nursing care of mouth and pressure areas.

Respiratory support

- Protect airway because vomiting is a risk: vomiting is particularly associated with opiates, benzodiazepines, alcohol and tricyclic anti-depressants.
- Respiratory depression might occur with opiates, benzodiazepines, alcohol, tricyclic anti-depressants.
- Monitor with pulse oximetry.
- Give oxygen: start with 60% humidified O₂.
- Loss of gag or cough reflex is the prime indication for intubation.

Cardiovascular support

- Watch for hypotension (systolic BP below 80 mmHg):
 - Mild: raise end of bed
 - Severe: use IV volume expanders, e.g. dextran
 - Very severe: insert CVP line to monitor fluid replacement
 - Measure urine output: aim for 0.5 mL/kg/h. Urine output is a useful guide to the adequacy of the circulation.
- Monitor ECG for arrhythmias.

What other problems might occur?**Blood pressure**

- Watch for hypotension (see above).
- Avoid vasopressant drugs because these might interact adversely with the poison.
- Less commonly, transient hypertension might be seen with amphetamine and cocaine.

Arrhythmias

- Might arise from hypoxia or metabolic acidosis.
- Bradycardia might occur with beta blockers, digoxin and organophosphorus compounds.

- Ventricular and supraventricular tachycardias occur due to theophyllines, tricyclic anti-depressants/phenothiazines (due to prolonged QT interval) cocaine, Ecstasy and amphetamine.

Hypothermia

- Can occur due to unconsciousness, especially with phenothiazines and barbiturates.
- Measure temperature rectally.
- Nurse under space blanket with warming, if needed, using water bottles.

Hyperthermia

- Can occur with amphetamines, Ecstasy and cocaine, selective serotonin reuptake inhibitors (SSRIs), salicylates and tricyclic anti-depressants.

What specific management procedures are there for overdoses?

Reducing absorption

- Gastric lavage: should only be used for life-threatening overdoses and only within the first hour for significant recovery of poison. Avoid lavage if corrosives, paraffin or petrol have been taken because of risk of inhalation. Always intubate if the patient is unconscious.
- Induced emesis: should not be used because it is ineffective at removal of poison and delays the use of activated charcoal.
- Activated charcoal: binds drugs in the intestine and is valuable for adsorbing most poisons but is most effective for aspirin, tricyclic anti-depressants and theophyllines. For most drugs do not use more than 1 h post-ingestion of poison or with an oral antidote (see also [Active elimination](#), below).

Active elimination

- Repeated doses of charcoal might enhance elimination for selected drugs even after the drug has been absorbed. This works for aspirin, barbiturates, quinine, theophylline and carbamazepine.
- Whole bowel irrigation using non-absorbable polyethylene glycol solution (not to be confused with ethylene glycol or anti-freeze) causes loose stool and forces bowel contents through, rapidly reducing absorption. This is not routinely used.
- Forced diuresis for salicylate poisoning is dangerous and should not be used.
- Urine alkalisation is mainly used for salicylate overdose (see [p. 403](#)).
- Haemodialysis helps in severe salicylate poisoning, barbiturates, ethylene glycol, alcohol and lithium poisoning.
- Haemoperfusion involves passing heparinised blood across absorbents such as charcoal. Works for barbiturates and theophylline.

Antagonising the influences of poisons

- Acetylcysteine or methionine replenishes cellular glutathione stores in paracetamol poisoning.
- Ethanol is a competitive inhibitor of alcohol dehydrogenase and is given in ethylene glycol (anti-freeze) poisoning. Fomepizole is also useful when ethanol is contraindicated, e.g. previous excess alcohol user or liver disease.
- Naloxone and opiates compete at the same receptor.

- **Progress.** The partner of this 25-year-old patient came to the MAU shortly after admission. He had found two empty boxes of diazepam which she had been taking for acute anxiety over the last few months. He said that her drug misuse might be related to her being made redundant a week ago. She did not require ventilation and woke up gradually. She was very tearful and apologetic and did not require psychiatric referral after counselling.

Benzodiazepine overdose

Benzodiazepines account for 40% of all overdoses.

Clinical features

- Drowsiness, ataxia, slurred speech, coma
- Respiratory depression and hypotension might occur.

Management – the problems

Respiratory depression or in combination with alcohol – vomiting and aspiration.

Treatment – supportive

- Protect airway and neurological observations.
- Gastric lavage is not required.
- Flumazenil is a benzodiazepine antagonist that can be used in severe overdose with marked respiratory depression only.
- Beware: seizures have followed flumazenil administration.
- Patients are usually fit to be discharged at 24 h.

PARACETAMOL (ACETAMINOPHEN) POISONING

Remember

- Paracetamol is consumed in 45% of overdoses in the UK
- As little as 7.5–15 g (15–30) tablets can cause severe hepatic necrosis.

Case history (2)

A young woman, aged 18, was brought into A&E by her boyfriend, who had found her drowsy. A tablet packet – possibly containing paracetamol tablets – and half a bottle of wine was found near her. They had argued the previous night and she had threatened suicide. He thought that she had taken the tablets 6 h ago. A past history of an eating disorder was elicited.

On examination she was very thin and had a GCS of 10. There were no other physical signs.

Investigations

- Baseline urea and electrolytes
- Liver function (including INR) and biochemistry
- Paracetamol and salicylate levels

This patient's paracetamol level was 140 mg/L and her salicylate level was < 10 mg at 6 h post-overdose. She was admitted to MAU.

Points to remember

- Nausea and vomiting are extremely common in first 24 h.
- Abdominal pain 24 h plus.
- Persistent nausea with subcostal pain usually indicates significant hepatic necrosis.
- Chronic alcohol excess or other enzyme-inducing drugs increase metabolism of drugs.
- Hypoglycaemia may occur.

Remember

Paracetamol is a constituent of co-proxamol or co-dydramol with an opiate.

Physical examination (Fig. 13.1)

- Check respiratory rate in case compound preparation consumed.
- Haematuria, proteinuria and loin pain after the first 24 h might indicate acute kidney injury (AKI).
- Later: liver flap and altered consciousness might develop 3 days plus.

Management – the problems

Paracetamol can cause hepatic necrosis, with maximum damage sustained 72–96 h after ingestion. Renal damage occurs even without major liver damage.

Information

Important points:

- Severe liver or renal damage: seek specialist advice
- Contact liver unit if INR > 3.0 or alanine aminotransferase > 1000 U/L, evidence of acidosis, encephalopathy or hypotensive with systolic less than 60 mmHg
- Hypoglycaemia might develop in first 48 h
- Alert renal physicians if serum creatinine rises
- There is evidence that administration of acetylcysteine, even in patients with established hepatic encephalopathy, might improve the prognosis

How should you manage this patient?

For general management, see p. 396.

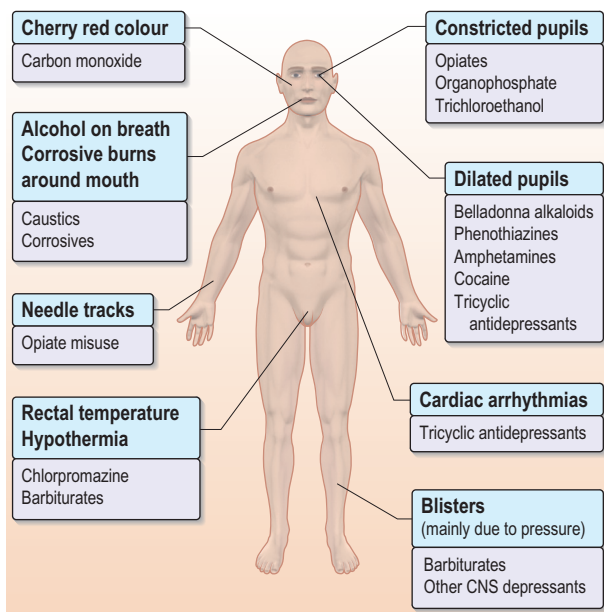


Figure 13.1 Physical signs of poisoning.

The treatment nomogram (Fig. 13.2)

- There are two lines on the nomogram: the normal and the high-risk treatment lines.
- The high-risk treatment line should be used for patients who are likely to be glutathione deplete, e.g. malnourished or HIV-positive patients.
- Alcohol dependent patients or those on enzyme inducers, e.g. phenytoin, rifampicin, carbamazepine, are also at high risk from lower levels of paracetamol.
- *This patient's* prior eating disorder and low body weight indicate that the high-risk treatment line should be used to interpret the paracetamol levels.

Information

Paracetamol overdose

- The National Poisons Information Service has received reports that the nomogram has not predicted paracetamol toxicity for some patients.
- Investigation indicates this relates to inaccurate history of timings, quantities and frequency of paracetamol overdose.

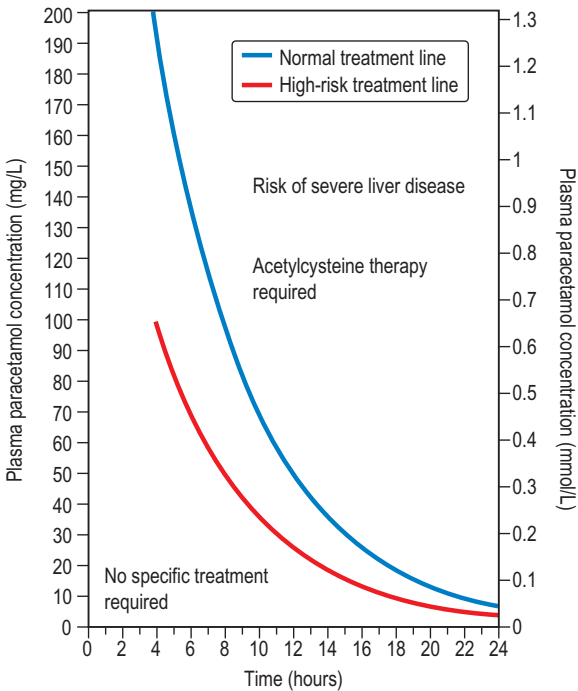


Figure 13.2 The treatment nomogram. From British National Formulary, with permission.

The antidotes – regime for treatment

Acetylcysteine by infusion

- Acetylcysteine 150 mg/kg in 200 mL 5% glucose over 15 min
- Then 50 mg/kg in 500 mL 5% glucose over 4 hours followed by 100 mg/kg in 1 L over 16 h. Total dose 300 mg/kg over 20–25 h.

What are the adverse reactions to acetylcysteine?

- Local itching and rashes at infusion sites.
- Systemic effects include nausea, flushing, angioedema, bronchospasm and hypotension. Treatment is with discontinuation of the infusion and an anti-histamine.

Once these effects have been resolved then the acetylcysteine infusion can be resumed at 100 mg/kg in 1 L over 16 h.

With a Glasgow Coma Score of 10, opiates were suspected in this patient and naloxone 0.8–2 mg IV was also given. As she responded to this, a naloxone infusion was started at a dose of 2 mg diluted in 500 mL with

the rate adjusted to clinical response as a single IV naxolone dose only lasts 30 min, as well as the acetylcysteine.

Intubation and ventilation were not required; pulse oximetry showed no impaired oxygenation.

Summary: how would you treat a paracetamol overdose?

If presentation within 8 h (as in this case)

- Gastric lavage or emesis up to 4 h post-ingestion.
- Use treatment nomogram at 4 h or later to guide use of acetylcysteine (see Fig. 13.2).
- If there is doubt about the timing, or if more than 12 g ingested, then treat with acetylcysteine immediately.
- If the 4-h paracetamol level is below the treatment line, discontinue acetylcysteine *except* in patients who are at high risk (see Fig. 13.2).
- If methionine or acetylcysteine is started within 8 h, the prognosis is good and patients can be considered for discharge at the end of the infusion if blood tests are normal.
- Prior to discharge check that INR and plasma creatinine are normal.
- Advise patient to return if vomiting ensues.
- Ensure that liaison with psychiatric services occurs.

If a patient presents at 8–24 h post-ingestion

- Patients presenting more than 8 h post-ingestion are at greater risk of hepatotoxicity: the efficacy of treatment with acetylcysteine declines *but still give it*.
- Individual response to paracetamol overdose can be variable and the validity of the treatment line beyond 15 h post-ingestion is not clear.
- If there is doubt about the timing of overdose, or if more than 12 g have been consumed, then treat with acetylcysteine immediately.
- At the end of the infusion, check that the INR and plasma creatinine are normal. If so, risk of damage is negligible and discharge can be planned.
- If INR or creatinine is abnormal, or the patient develops symptoms, continue to monitor these blood tests till normal.

If a patient presents 24 h plus post-ingestion

- The treatment remains controversial but there is evidence of benefits of acetylcysteine in those who develop hepatic encephalopathy.
- All should have INR, creatinine, BM Stix glucose and arterial pH monitored.
 - **Progress.** This woman was given acetylcysteine and her INR monitored within the normal range. She was discharged after being seen by the duty psychiatrist with an urgent referral to Mental Health Services.

SALICYLATE OVERDOSE

Case history

A 16-year-old girl was brought to A&E by her parents following an episode of nausea, followed by severe vomiting. Her parents then found packs of Sol Aspirin tablets in her bedroom, which she said she had taken because of difficulties with friends at school. She

Case history (continued)

also complained of tinnitus and deafness. The parents think the aspirin ingestion occurred about 4 hours ago.

On examination she is hyperventilating with peripheral vasodilation, profuse sweating and tachycardia, suggesting a moderate/severe **salicylate overdose**. She was transferred to MAU.

- Aspirin is rapidly absorbed: usually peaks at 4 h.
 - <150 mg/kg bodyweight causes mild toxicity
 - 150–130 mg/kg bodyweight causes moderate toxicity
 - 300–500 mg/kg bodyweight causes severe toxicity.
- Beware modified-release formulations: these can prolong absorption.
- Aspirin itself might delay gastric emptying.

Clinical features

- Early features include nausea, vomiting, tinnitus or deafness (severe overdose), sweating and hyperventilation.
- Later features include Kussmaul's respiration, confusion, coma, fits and renal impairment.

Investigations

- Blood gases reveal a respiratory alkalosis.
- Plasma salicylate measured after 4 hours.

Management – the problems

- Aspirin delays gastric emptying.
- People who appear well might have very high levels.
- Early hypokalaemia and respiratory alkalosis may be replaced after 4–6 h by metabolic acidosis due to salicylate.
- Hypo-prothrombinaemia might occur (increased prothrombin time/INR).

Treatment

- Gastric lavage was not attempted as tablets taken 4 hours previously.
- Repeated doses of charcoal enhance elimination.
- Intravenous fluids with potassium supplements to correct dehydration, hypokalaemia and improve urine flow were given.
- Forced alkaline diuresis should not be used.
- Urine alkalinisation was used when plasma salicylate levels were found to be 620 mg/L. 8.4% bicarbonate (approx. 225 mL) in 1 h with careful monitoring.
- Haemodialysis should only be used when salicylate level is > 700 mg/L.
 - **Progress.** This young girl was kept in hospital for 3 days, during which time she fully recovered and her blood gases and electrolytes returned to normal. She was seen with her parents by the Psychiatric Department but further counselling was not thought to be necessary.

Information

Risk factors for death from salicylates:

- Age over 70 years
- CNS features
- Metabolic acidosis
- Hyperpyrexia
- Late presentation
- Pulmonary oedema
- Salicylate concentrations > 700 mg/L (5.07 mmol/L)

Tricyclic anti-depressant overdose

These have become less common since the selective serotonin reuptake inhibitors became available (much safer). Features of overdose are mainly due to anti-muscarinic and alpha blocking adverse effects. Arrhythmias occur due to prolongation of the QT interval.

Clinical features

- Drowsiness, confusion but rarely unconsciousness
- Blurred vision due to fixed dilated pupils
- Sinus tachycardia with long QT interval
- Ventricular arrhythmias
- Hypotension
- Hypothermia
- Hyper-reflexia and extensor plantars occur
- Agitation, visual and auditory hallucinations are common during recovery
- Seizures occur in less than 5%.

Treatment – supportive

- Gastric lavage up to 4 h post-ingestion for life-threatening amount of drug.
- Activated charcoal reduces absorption of tricyclics; anti-cholinergic action delays gastric emptying.
- Cardiac monitor and watch for hypotension.
- Neurological observations.
- Seizures might require IV diazepam 10 mg.
- Ventricular arrhythmias due to prolonged QT interval should not be treated with anti-arrhythmics but with under-drive or over-drive temporary pacing.
- Rarely, heart block and electrical mechanical dissociation have occurred.
- Occasionally, metabolic acidosis ensues – this should be corrected if pH of 7.0 or less develops using 1.4% sodium bicarbonate.

COCAINE

Cocaine (Fig. 13.3) can be inhaled (snorted), injected or swallowed or separated from its hydrochloride base and melted as crack. Binges with cocaine can last 24–96 h.

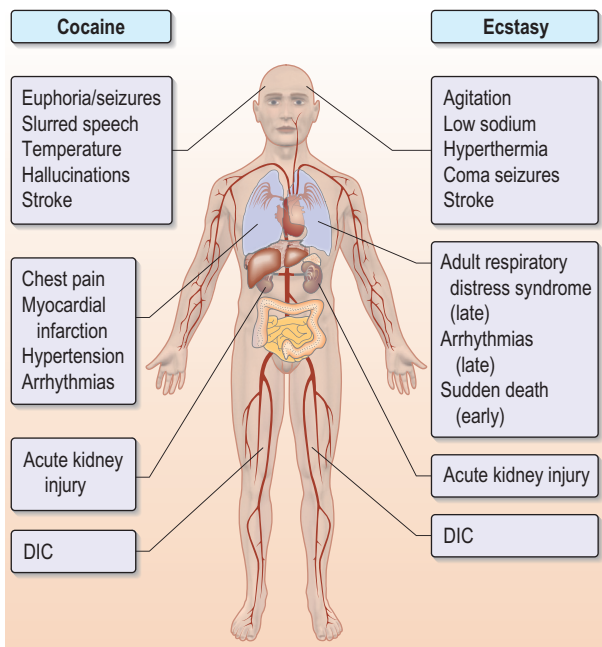


Figure 13.3 Features of cocaine and Ecstasy abuse.

Case History

A 32-year-old man is brought to A&E by his friends who were all at a party together. A large amount of alcohol was drunk and some drugs had been used, mainly cannabis and Ecstasy. The patient had been found semi-conscious and when his friends tried to move him he seemed to have no movement in the left side of his body.

On examination he has a Glasgow Coma Score of 9. He has signs of a left hemiparesis.

Remember

If a young person presents with a stroke or myocardial infarction, cocaine overdose should always be looked for.

Clinical features of cocaine toxicity

- Euphoria, slurred speech, dilated pupils
- Pyrexia, sinus tachycardia and hallucinations (auditory, tactile and olfactory)
- Hypertension (may be severe) rarely causing haemorrhagic stroke, hyperventilation
- Myocardial infarction may occur in 6% of those with chest pain
- Ventricular arrhythmias, seizures
- Later kidney injury, disseminated intravascular coagulation.

Immediate plan

- ABCDE
- Admit to HDU
- Blood tests (Hb, WCC, U&Es glucose, INR)
- Arrange urgent CT scan. This shows evidence of cerebral haemorrhage so any further active treatment is not required. He was transferred to the Stroke Unit (see p. 476).

Ecstasy (see Fig. 13.3)

Ecstasy is an amphetamine derivative known as MDMA, which stimulates the sympathetic nervous system, and prevents neuronal reuptake of catecholamines, dopamine and serotonin (5HT).

Clinical features

- Agitation, profound dehydration, low sodium due to excess water consumption or anti-diuretic hormone.
- Early arrhythmias (supraventricular or ventricular) occur and can cause sudden death.
- Nausea, vomiting, muscle pain, sinus tachycardia and visual hallucinations.
- Hypertension (might be severe) rarely causing haemorrhagic stroke, chest pain, hyperventilation.
- Hyperthermia, coma, seizures, rhabdomyolysis, rarely fulminant hepatic failure.
- Later: acute kidney injury, disseminated intravascular coagulation, acute respiratory distress syndrome.

Investigations

- Baseline: full blood count, urea and electrolytes, glucose, liver function
- 12-lead ECG
- Paracetamol and salicylate levels at 4 h or thereafter if coexistent overdose suspected
- Urine screen for drugs of abuse
- Imaging, e.g. brain CT

Treatment – supportive

- Activated charcoal reduces absorption within 1 h.
- Early hyponatraemia due to excessive water consumption by Ecstasy users should be looked for before rehydration.
- Cardiac monitor and watch for hypertension.
- Treat agitation or seizures with IV diazepam 10 mg.

- Hyperthermia $> 39^{\circ}\text{C}$ can be reduced by 1 litre of cold saline. If temperature does not respond, IV dantrolene might help.
- Ventricular arrhythmias should be treated with anti-arrhythmics.

GAMMAHYDROXYBUTYRIC ACID (GHB)

GHB has been used by bodybuilders and for weight reduction. It was sold as a salt, which forms a colourless liquid in water. It is no longer available legally. The seaweed-like taste can be impossible to detect when added to an alcoholic drink. GHB has been used to facilitate 'date rape'. Street names includes 'scoop', 'easyday' and 'liquid X'.

Clinical features

- History might indicate no intent or knowledge of consumption of any drug.
- Initial euphoria, disinhibition, agitation, confusion, nausea and diarrhoea progressing within 1 h to drowsiness and unconsciousness (potentiated by alcohol).
- Nausea, vomiting, muscle pain, sinus tachycardia, and rarely seizures.
- Bradycardia, respiratory depression and even Cheyne–Stokes respiration might rarely occur.
- Be alert to the possibility that such patients might have suffered sexual assault.

Investigations

For GHB consumption

- Baseline full blood count, urea and electrolytes (may reveal hypernatraemia and hypokalaemia), blood glucose and liver function
- Blood gases if patient is unconscious or respiratory depression occurs (metabolic acidosis may occur)

Treatment of GHB consumption – supportive

- Activated charcoal reduces absorption within 1 h: observe for a minimum of 2 h even if apparently clinically much improved.
- Monitor blood pressure, heart rate and pulse oximetry.
- Treat seizures with IV diazepam 10 mg.
- Bradycardia associated with hypotension should be treated with IV atropine.

Significant websites

www.toxbase.co.uk

Toxbase – Database of UK National Poisons Information Service

www.toxinz.com

Database of the New Zealand Poisons Centre

www.toxnet.nlm.nih.gov

National Library of Medicine's Toxnet

www.who.int/ipcs/poisons/centre/directory/en

Contact details of all poisons centres worldwide

www.wikitox.org

Home of the Clinical Toxicology Teaching Resource Project

- **Progress.** This young man continued to deteriorate and died 33 hours after admission. It was later found that he tried smoking cocaine for the first time.

INSECT STINGS AND BITES

Case history

A 24-year-old had been cleaning a pond in the summer when she was stung by a wasp. A few minutes later she felt unwell and had to lie down as she felt faint. She then noticed some difficulty in breathing and felt a 'tightening' of her face. After 45 minutes her symptoms improved.

- **Diagnosis.** Mild anaphylactic reaction to wasp sting. She made a complete recovery.

Anaphylactic reactions can be fatal

Reactions to penicillin: 1 death in every 7.5 million injections
 Bee and wasp stings 1 : 200 stings severe reactions
 (USA 60–80 deaths per year)
 (UK 5–10 deaths per year)

ANAPHYLACTIC SHOCK

Typically follows second or third challenge.

History

- Exposure to insect bite, bee or wasp sting, seafood, nuts, drugs (e.g. penicillin, NSAIDs) or contrast media
- Dizziness, wheeze and facial swelling
- Past history of allergy.

Examination

- Facial oedema
- Tachycardia, hypotensive
- Stridor due to laryngeal oedema
- Bronchospasm.

Immediate management

- Ensure clear airway and establish large-bore venous access.
- Oxygen 35% unless hypoxic.
- If there is serious hypoxia and stridor, tracheostomy might be required.
- Lie flat and elevate legs.
- Cardiovascular observations.
- Administer 0.5 mg adrenaline (epinephrine) intramuscularly (not IV) to create depot support for the circulation.

- Repeat after 5 min if still hypotensive.
- Follow with anti-histamine: chlorphenamine 10 mg IV.
- Then hydrocortisone 100 mg IV.

Further management

- If persistent hypotension, infuse plasma expander e.g. 1 litre of Haemaccel.
- Salbutamol 2.5–5 mg nebulised or IV for bronchospasm or continued shock.
- An aminophylline infusion for continuing bronchospasm.
- Always identify precipitant.
- Advise on medic-alert bracelet.
- Provide the patient with adrenaline (epinephrine) Miniject 0.3 mg and tuition to inject in thigh in the event of exposure to allergen. This should be carried with the patient at all times.

Prevention

- This is the best.
- Avoid triggering factor, e.g. food, stings.
- Patient education is vital.
- Self-administered adrenal (epinephrine). Patients should always carry pre-loaded syringes.

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DIABETES MELLITUS

Diabetes mellitus is a syndrome of chronic hyperglycaemia due to relative insulin deficiency or resistance or both.

Case history (1)

You are telephoned by a GP who has seen a 50-year-old man in his surgery complaining of thirst and polyuria. His venous blood glucose is 24 mmol/L. He is tired but otherwise well.

What are the key decisions in this case?

- Does this patient need admission?
- Does he need insulin?
- What is the immediate management?

The likelihood is that this patient has **type 2 diabetes** (Table 14.1). The risk of ketoacidosis is small and he will not need admission unless he is either ketotic (ketonuria 3+) or is very dehydrated.

This patient should be advised to avoid sweet drinks (especially sweetened canned drinks) and an appointment arranged for him to attend a diabetic outpatient clinic. Contact the diabetic liaison nurse in your hospital and arrange for the patient to be seen urgently.

Indications for admission

- Severe dehydration (may have hyperosmolality).
- Intercurrent illness such as pneumonia or UTI.
- 3+ ketonuria.
- Tachycardia or tachypnoea.

Information

Diagnostic criteria for diabetes mellitus:

- Fasting venous plasma glucose > 7.0 mmol/L (126 mg/dL) after 8-h fast*
- Random venous plasma glucose > 11.1 mmol/L (200 mg/dL)*
- An HbA1c of > 6.5% (48 mmol/mol) has recently been approved for diagnosis (Table 14.2)

*Two readings are required for asymptomatic individuals. Note also:

- Impaired fasting glucose: 5.6–6.9 mmol/L
- Impaired glucose tolerance: > 7.8 and < 11.1 mmol/L; 2 h after 75 g oral GTT.

An oral glucose tolerance test is only required for borderline cases.

Table 14.1 The spectrum of diabetes: a comparison of type 1 and type 2 diabetes mellitus

	Type 1	Type 2
Epidemiology	Younger (usually < 30 years of age) Usually lean Increased in those of Northern European ancestry Seasonal incidence	Older (usually > 30 years of age) Often overweight All racial groups. Increased in peoples of Asian, African, Polynesian and American-Indian ancestry
Heredity	HLA-DR3 or DR4 in > 90% 30–50% concordance in identical twins	No HLA links ~ 50% concordance in identical twins
Pathogenesis	Autoimmune disease Islet cell autoantibodies Insulinitis Association with other autoimmune diseases Immunosuppression after diagnosis delays beta-cell destruction	No immune disturbance Insulin resistance
Clinical	Insulin deficiency May develop ketoacidosis Always need insulin	Partial insulin deficiency initially May develop hyperosmolar state Many come to need insulin when beta-cells fail over time
Biochemical	Eventual disappearance of C-peptide	C-peptide persists

Note: there is a significant rise in the incidence of young patients with type 2 diabetes mellitus, especially in the obese and in Asian populations.

- **Progress.** At the Diabetic Clinic the diabetic nurse explained life-style changes that are an essential part of treatment, i.e. stopping smoking, losing weight with a diet and exercise. The nurse arranges for an appointment for this patient to be checked by the doctor and for eye testing. He was also started on Metformin 500 mg daily, increasing to 1.5 g daily.

Table 14.2 HbA1c – conversion of percentage values to mmol/mol

DCCT HbA1c %	IFCC HbA1c mmol/mol
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75
10.0	96

DCCT, Diabetes control and complication trial.

IFCC, International Federation of Clinical Chemistry.

Case history (2)

You are telephoned by a GP who has seen a 17-year-old man in his surgery complaining of thirst and polyuria. He has recently lost 8 kg in weight. His blood glucose is 31 mmol/L.

The key decisions are again:

- Does this patient need admission?
- Does he need insulin?
- What is the immediate management?

This patient is much more likely to be presenting with early **type 1 diabetes** and might not be ketotic yet because he could still have a degree of residual beta cell function (the ‘honeymoon’ phase). Again, assessment of ketosis, acidosis and dehydration must be made to determine whether he needs admission. He should be seen within 24 h either by the diabetic liaison nurse or in hospital to commence insulin. If there is any doubt, the patient should be seen in A&E immediately.

- **Progress.** At the Diabetic Clinic the patient was dehydrated with mild ketosis. He was admitted to MAU to commence insulin therapy.

DIABETIC KETOACIDOSIS (DKA)

Case history (3)

A 21-year-old woman presents to A&E having been generally unwell for 2 weeks and having been treated for a urinary tract infection by her doctor.

Continued

Case history (3) (continued)

Examination reveals severe dehydration, a tachycardia of 120 bpm and a blood pressure of 90/50 mmHg. The nurses have checked her finger-prick blood glucose (BM Stix) and found it to be 30 mmol/L.

- **Diagnosis.** Diabetic ketoacidosis.

How do patients present with ketoacidosis?

- Unwell \pm intercurrent illness (e.g. bacterial or viral infection)
- Polyuria and polydipsia
- Hyperventilation or dyspnoea
- Vomiting \pm abdominal pain
- Impaired conscious level.

Patients known to have type 1 diabetes mellitus most commonly develop ketoacidosis when insulin is omitted because of missed meals during an intercurrent illness (e.g. gastroenteritis). Patients become rapidly dehydrated (Fig. 14.1) and acidotic (over hours). Tachypnoea or Kussmaul respiration (a deep sighing respiration) is prominent, with the smell of ketones on the breath. It is the fall in pH that causes coma.

The blood glucose might not be particularly high and severe acidosis be present, with glucose values as low as 10 mmol/L. This might be due to recent self-administration of insulin, which is insufficient alone to correct the acidosis in the presence of dehydration.

Assessment of severity

Poor prognostic features include:

- Impaired conscious level (indication for urgent intubation)
- pH < 7.0
- Oliguria
- Low serum potassium at presentation.

Investigations

- Blood glucose
- Arterial blood gases and pH
- Urea and electrolytes – bicarbonate in venous blood < 12 mmol/L – severe acidosis
- Urinalysis (ketones strongly positive + + +)
- Plasma ketones – test with ketostix
- Full blood count
- Blood \pm urine cultures
- CXR
- ECG and cardiac enzymes

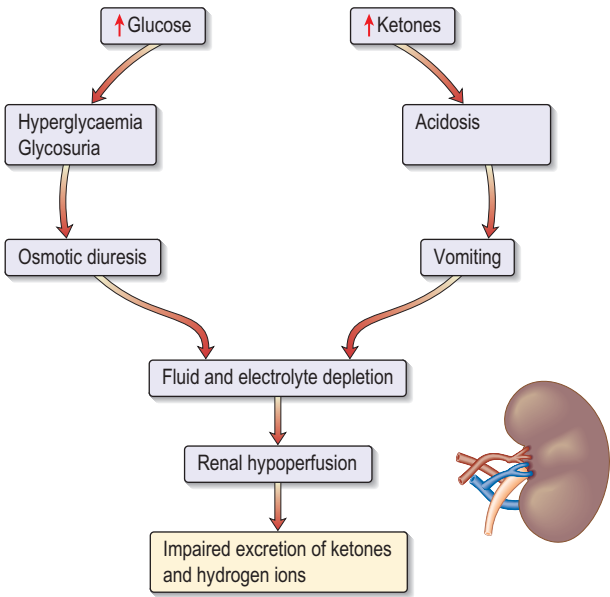


Figure 14.1 Dehydration occurs during ketoacidosis as a consequence of two parallel processes. Hyperglycaemia results in osmotic diuresis, and hyperketonaemia results in acidosis and vomiting. Renal hypoperfusion then occurs and a vicious circle is established as the kidney becomes less able to compensate for the acidosis.

Management: general measures

- Admit to HDU.
- Insert a central line in patients with a history of cardiac disease/renal impairment/autonomic neuropathy or the elderly.
- An arterial line to monitor ABGs and plasma potassium.
- Nil by mouth for at least 6 h.
- Nasogastric tube: if there is impaired conscious level, to prevent vomiting and aspiration.
- Urinary catheter: if no urine for 2 hours or serum creatinine is high.
- Low molecular weight heparin: enoxaparin 40 mg SC daily.

Remember

Management of DKA requires fluid, insulin, potassium and *care*.

Management: fluid replacement

Severely shocked patients may require colloid to restore circulating plasma volume. [Table 14.3](#) shows examples of blood values in severe ketoacidosis

and compares these with those seen in the hyperosmolar, hyperglycaemic state described on page 418.

The guidelines for fluid replacement are shown in Table 14.4. These are applicable for young patients.

- When blood glucose falls to less than 12 mmol/L convert to a 5% glucose infusion. This will enable the insulin infusion to be continued. Continued insulin is required to inhibit ketone production.
- Continue with IV fluids 1 L every 4–6 h until rehydrated and ketosis resolves (~24 h).

Table 14.3 Examples of blood values

	Severe ketoacidosis	Hyperosmolar, hyperglycaemic state
Na ⁺ (mmol/L)	140	155
K ⁺ (mmol/L)	5	5
Cl ⁻ (mmol/L)	100	110
HCO ₃ ⁻ (mmol/L)	5	25
Urea (mmol/L)	8	15
Glucose (mmol/L)	30	50
Arterial pH	7.0	7.35

The normal range of osmolality is 285 to 300 mOsmol/kg. It can be measured directly, or can be calculated approximately from the formula:

$$\text{Osmolality} = 2(\text{Na}^+ + \text{K}^+) + \text{glucose} + \text{urea}$$

For example, in the example of severe ketoacidosis given above:

Osmolality = $2(140 + 5) + 30 + 8 = 328$ mOsmol/kg, and in the example of non-ketotic hyperosmolar coma:

$$\text{Osmolality} = 2(155 + 5) + 50 + 15 = 385 \text{ mOsmol/kg}$$

The normal anion gap is less than 17. It is calculated as $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$. In the example of ketoacidosis, the anion gap is 40, and in the example of non-ketotic hyperosmolar coma the anion gap is 20. Mild hyperchloraemic acidosis may develop in the course of therapy. This will be shown by a rising plasma chloride and persistence of a low bicarbonate even though the anion gap has returned to normal.

Table 14.4 Guidelines for average fluid replacement in young patients

Volume	Duration/timing
1 L 0.9% saline + 20 mmol/KCl	Over the first 30 min
1 L 0.9% saline + 20 mmol/KCl	Over next 1 h
1 L 0.9% saline + 20 mmol/KCl	Over next 2 h
1 L 0.9% saline + 20 mmol/KCl	Over next 4–6 h

Management: insulin regimen

- Add 50 units of soluble insulin to 50 mL 0.9% saline and administer by intravenous infusion; this equates to 1 U/mL.
- Commence at 6 U/h and continue at 3 U/h after venous glucose falls to < 11.5 mmol/L.
- Glucose must then be administered to prevent hypoglycaemia (see above).
- Continue IV insulin infusion until ketosis resolves, the patient is eating and for 2–4 h after the first SC dose of soluble insulin.

Management: potassium replacement (Table 14.5)

Total body potassium can be depleted by approximately 1000 mmol and the plasma potassium falls rapidly as potassium shifts into the cells under the action of insulin. Use less potassium in patients with renal impairment or oliguria.

- Monitor serum $[K^+]$ every 2 h initially then every 4 h until stable.
- Use premixed potassium-containing infusions wherever possible.

Management: acidosis

- If the pH < 7.0: isotonic (1.26%) sodium bicarbonate given at a rate of 500 mL over 4 h is safe. If the pH > 7.0, bicarbonate need not be given.

Assessment during treatment

- Remember the role of insulin is primarily to suppress ketogenesis rather than to lower blood glucose.
- Blood glucose (BM Stix every hour, laboratory blood glucose 4-hourly).
- Plasma potassium every 4 h: the main risk is hypokalaemia.
- Repeat ABGs after 2 h. A calculated anion gap (needs chloride estimation) may be adequate for monitoring.

Remember**Causes of death in DKA:**

- Hyperkalaemia
- Aspiration due to gastric stasis
- Cerebral oedema due to acidosis ± overhydration
- Hypokalaemic respiratory arrest

Table 14.5 Potassium replacement in patients with diabetic ketoacidosis

Serum potassium (mmol/L)	Amount of KCl (mmol/hour)
<3	40
3–1	30
4–5	20
5–6	10
> 6	Stop KCl

- **Progress.** This patient started eating and treatment with SC insulin after 48 hours. She was shown a video on diabetes and its self management. She was helped with her insulin injections and discharged on the 6th day with support from the Community Diabetic Nurse.

HYPEROSMOLAR HYPERGLYCAEMIC STATE

Case history (4)

A 60-year-old woman is referred to A&E following a collapse. She has been generally unwell for the last year. Her husband confirms that she has had polyuria and polydipsia with nocturia of three to four times every night. Over the last month, she has started using sugar drinks to build herself up because she has been losing weight.

Examination reveals an extremely dehydrated woman with increased tissue turgor. Pulse 100 regular, BP 100/60. JVP not visible. Glasgow coma scale 12.

Investigations revealed:

Na⁺ 165; K⁺ 5.9; U 24.7; Cr 170; Bicarb 20; Glucose 64 mmol/L; pH 7.31; pCO₂ 4.7 kPa; pO₂ 11.2 kPa; plasma osmolality $2 \times (165 + 5.9) + 64 + 24.7 = 429.7$ mOsmol/kg.

These findings are typical of **hyperosmolar hyperglycaemic state** (see Table 14.3).

Information

Calculation of osmolality:

$2 \times (\text{Na}^+ + \text{K}^+) + \text{glucose}$ (normal range 285–300 mOsmol/kg)

How should this patient be managed?

Hyperosmolar hyperglycaemic state occurs in older patients with type 2 diabetes. It is characterised by a very high glucose, a relatively normal acid-base balance and high plasma osmolality. These patients are also at increased risk of venous and arterial thromboses. The mortality is higher than for DKA. This patient's biochemistry has been slowly getting worse over many weeks, so normalisation must be equally slow.

Remember

Ketones can be found in the urine in any starved person.

How do patients present?

- The patient is middle aged or elderly
- Insidious onset of polyuria and polydipsia

- Severe dehydration
- Altered conscious level
- Most middle-aged or elderly patients have not previously been diagnosed with diabetes
- Respiration is usually normal
- Presentation is usually precipitated by infection, stroke or myocardial infarction.

Diagnosis and investigations

- Plasma glucose: usually > 40 mmol/L.
- U&Es: significant hypernatraemia occurs but this is masked by the high glucose. The $[Na^+]$ usually increases as the venous glucose and therefore the extracellular colloid osmotic pressure falls and water moves into the intracellular space.
- Arterial blood gases: relatively normal.
- Plasma osmolality: typically > 350 mOsmol/kg.
- Estimate corrected sodium to evaluate water loss as a result of hyperglycaemia (see Information box).
- FBC: may show polycythaemia, dehydration or a leucocytosis from infection.
- CK: cardiac ischaemia or rhabdomyolysis.
- Troponins.
- ECG: for myocardial infarction or ischaemia.
- CXR: for signs of infection.
- Urine for urinalysis, microscopy and culture.

Information

Calculation of corrected sodium concentration: Add 2.0 mmol/L to the measured serum sodium for every 5 mmol/L increase in glucose concentration. Thus a fall in glucose from 50 to 25 mmol/L will be accompanied by a rise in $[Na^+]$ of 10 mmol/L.

Remember

The principal cause of death and morbidity in hyperosmolar hyperglycaemic state is arterial and venous thrombosis due to the hyperosmolar state.

Assessment of severity

- The degree of consciousness correlates most closely with plasma osmolality. Coma is usually associated with an osmolality of greater than 400 mOsmol/kg.
- A coexistent lactic acidosis considerably worsens the prognosis.

How would you manage this patient?

General treatment measures

- Aim to correct the high osmolality with fluid and insulin over 48–72 h. Avoid fluid overload and insert a central venous line if cardiac problems.

- Manage as for DKA except:
 - 0.9% saline is the standard fluid for replacement given slowly
 - If $[Na^+]$ is > 150 mmol/L then use 5% glucose
 - Ensure slow correction of serum sodium (see p. 229)
 - Start insulin at 3 U/h as patients are often sensitive to insulin
 - Anti-coagulate with SC enoxaparin 40 mg daily unless contraindicated
 - Urinary catheter if oliguria is present, or serum creatinine is high.
- When blood glucose is less than 10 mmol/L, commence a 5% glucose infusion.
- Once stable, stop insulin therapy and commence oral hypoglycaemic agents or diet alone.
 - **Progress.** This patient was discharged on metformin 1 g daily and instructed on lifestyle changes, e.g. controlling weight and an urgent appointment with the Community Diabetic Nurse.

HYPOGLYCAEMIC COMA

Case history (1)

A 25-year-old man is brought to A&E by the police, having been found behaving abnormally. He is aggressive and irrational and attempts to punch the staff. He is restrained and a MedicAlert bracelet is found under his shirt indicating that he has diabetes. A finger-prick glucose reads 'low'.

- **Diagnosis. Hypoglycaemia.**

Always consider hypoglycaemia in confused patients and check a blood glucose using a glucostix (or BM Stix), confirming with a laboratory determination wherever possible. The most common cause of coma in a patient with diabetes is hypoglycaemia due to drugs. The long-acting sulphonylureas, such as glibenclamide, or long-acting insulins, such as Isophane, are prone to do this. Patients who are *not* known to have diabetes but who are hypoglycaemic should have a laboratory-determined blood glucose and blood saved (serum) for insulin and C-peptide determination (to diagnose insulinoma or factitious drug administration).

How do patients present? (Table 14.6)

Patients with tightly controlled diabetes can have frequent episodes of hypoglycaemia and can become desensitised to sympathetic activation. These patients can develop neuroglycopenia before sympathetic activation and complain of 'loss of warning'. Use of beta blockers can also minimise the warning signs of hypoglycaemia by blocking the features of an activated sympathetic nervous system.

Conversely, patients with poorly controlled diabetes develop sympathetic signs early and avoid these by running a high blood glucose. They complain of 'being hypo' when their blood sugar is normal or high. They do not require glucose.

Table 14.6 Presentation of patients with hypoglycaemic coma

Sympathetic overactivity (glucose < 3.5 mmol/L)	Neuroglycopenia (glucose < 2.6 mmol/L)
Tachycardia	Confusion
Palpitations	Slurred speech
Sweating	Localised neurological impairment
Anxiety	Coma
Pallor	
Tremor	
Cold extremities	

Information

Patients with type 2 diabetes who are on diet alone or metformin (but no insulin or sulphonylureas) *cannot* become hypoglycaemic.

Assessment of severity

- Hypoglycaemia in a patient with diabetes is defined as < 3.5 mmol/L.
- A 'mild' episode requires intervention by the patient.
- A 'severe' episode might lead to coma and requires treatment by a third party.

Investigations

Patients with diabetes with frequent hypoglycaemic attacks:

- Urea and electrolytes: hypoglycaemia is more common in diabetic nephropathy because the kidney is one of the sites of insulin metabolism
- Thyroid function tests: hypothyroidism is associated with type 1 diabetes mellitus and impairs counter-regulation
- 09:00 cortisol ± short ACTH (tetracosactide) stimulation test: hypoadrenalism reduces hepatic glycogen stores (see p. 443)
- Take an alcohol history
- Consider deliberate self-harm

How would you manage hypoglycaemia?

Conscious patient

Treat with 15–20 g carbohydrate, i.e. four glucose tablets, or glucose drink.

Unconscious patient

- Take blood sample.
- Give:
 - 75 mL 20% glucose IV *or*
 - 1 mg glucagon intramuscularly.

- Do not use 50% glucose in peripheral veins.
- Once recovered, give 1–2 slices of bread or 2–4 biscuits.
- Admit the patient if the cause is a long-acting sulphonylurea or a long-acting insulin and give a continuous infusion of 10% glucose (e.g. 1 litre 8-hourly) and check glucose hourly or 2-hourly.
- Patients should regain consciousness or become coherent within 10 min, although complete cognitive recovery might lag by 30–45 min. Do not give further boluses of IV glucose without repeating the blood glucose. If the patient does not wake up after 10 min or more, repeat the blood glucose and consider another cause of coma – stroke or a head injury during their confused state.

Hypoglycaemia in the non-diabetic patient

Hypoglycaemia in patients without diabetes is rare and always needs investigation – usually as an inpatient. Always:

- Confirm the hypoglycaemia with a laboratory sample before treatment.
- Take a simultaneous serum sample for insulin and C-peptide (the fragment of proinsulin that is found in endogenous insulin), sent urgently to the laboratory for centrifugation and separation.

Causes of hypoglycaemia

- Drugs:
 - Surreptitious insulin or sulphonylurea ingestion
 - Ethanol
 - Quinine
 - Pentamidine
 - Disopyramide
 - Prescription errors, e.g. chlorpropamide for chlorpromazine (ask for all drugs to be brought in).
- Tumours:
 - Insulinoma
 - Retroperitoneal sarcomas and other malignancies.
- Liver failure.
- Hypopituitarism, causing ACTH, GH and TSH deficiency.
 - *Progress.* This patient responded to IV glucose and quickly returned to normal. He explained that he was out with friends last night and forgot to eat but continued to drink alcohol. He thinks he may have given himself the wrong amount of insulin as he overslept and was late for work.

SICK DIABETIC PATIENT

Case history

A 40-year-old man with a 15-year history of type 1 diabetes mellitus and previously documented proteinuria is referred from A&E with vomiting and feeling generally unwell. Glucose was 20 mmol/L, electrolytes were normal and blood gases did not support diabetic ketoacidosis (pH 7.4; bicarbonate 20 mmol/L). An

Case history (continued)

ECG shows evidence of evolving anterior myocardial infarction. This is the typical presentation of a 'silent MI'. Chest pain is frequently atypical or absent in diabetes due to small fibre neuropathy. The other major cause of this type of non-specific presentation is occult infection and often further investigations are required:

Investigations

- FBC
- Urea and electrolytes
- ABG
- CXR
- MSU
- ECG
- Blood cultures

Other investigations to consider later if occult infection is suspected:

- Abdominal US or abdominal CT scan
- Tc bone scanning
- Labelled white cell scan

Treatment/progress

This patient has a diagnosis of STEMI and requires immediate therapy with aspirin 300 mg chewed and clopidogrel 300 mg oral gel. He was immediately transferred to the Coronary Care Unit for further assessment and possible percutaneous coronary intervention, which is instantly available (p. 285). His diabetes was initially controlled on insulin infusion because he was nil by mouth for the cardiac procedures (Table 14.7). The infusion was continued until the patient was eating and drinking. Insulin treatment has been proven to improve outcome in patients with diabetes in the immediate period after myocardial infarction.

Once eating and drinking, the patient can be converted back to his or her usual insulin regimen or, if tight glycaemic control is essential, on to $\times 4$ daily insulin (see below), which gives greater ease of adjustment.

Remember

Always carefully inspect the feet in unwell diabetic patients – infected ulcers are common and may be painless.

Table 14.7 Intravenous infusion insulin management of type 1 diabetes mellitus in hospital

Level of blood glucose (measured hourly)	Insulin infusion (units per hour)
< 4.0 mmol/L	0.5
4.0–7.0 mmol/L	1
7.1–9.0 mmol/L	2
9.1–11.0 mmol/L	3
11.1–14.0 mmol/L	4
14.1–17.0 mmol/L	5
17.1–28 mmol/L	6
> 28 mmol/L	8

Note: the above is only a guide and insulin doses should be adjusted upwards if the patient is known to have a high insulin requirement, and always reviewed regularly to see if the doses are appropriate. The aim is to keep blood glucose in the 7–9 region.

Protocol for converting diabetics from intravenous to subcutaneous insulin

- Calculate total dose over last 24 h.
- Give 25% of total as soluble insulin 30 min before each meal (i.e. $\times 3$ daily).
- Give 25% of total dose as intermediate-acting isophane insulin at 22:00.
- Monitor blood glucose fasting and 2 h after meals (post-prandial) – each finger-prick glucose measures the adequacy of the previous dose.
- Aim for glucose < 10 mmol/L post-prandial and < 8 mmol/L fasting.
- Do not discontinue IV insulin until 1–2 h *after* the first subcutaneous insulin dose is administered, because IV insulin has a half-life of only 3 min.

MANAGEMENT OF NEW TYPE 2 DIABETIC PRESENTING FOR SURGERY

Case History

You are asked to see a 50-year-old man with no previous history of diabetes who is admitted for coronary artery bypass surgery and found to have a blood glucose of 13 mmol/L. This patient has suffered from angina for 5 years but he still has symptoms on maximal medical therapy. He has had coronary angiography which shows triple vessel disease and his cardiologist has recommended surgery rather than percutaneous coronary intervention.

How would you manage this patient?

- Ask about symptoms of diabetes, e.g. thirst, polyuria, lack of energy.
- Check that a laboratory glucose has been sent to confirm the diagnosis of diabetes (random glucose 13.4 mmol/L).
- Discuss patient's angina symptoms and discuss with cardiologist the urgency of CABG surgery.
- It is agreed by all, including the patient, that his diabetes should be treated and blood sugar controlled before surgery is performed.
- The patient is referred to the Diabetic Liaison Nurse for assessment and discussion of treatment as an outpatient.

Remember

Always get diabetes under control before patients undergo surgery unless this is an emergency.

Information

Assessment of new patients with diabetes

- Biochemical assessment of long-term glycaemic control (e.g. HbA1c)
- Measure body weight
- Measure blood pressure
- Measure plasma lipids
- Measure visual acuity
- Examine the retina through dilated fundi (ophthalmoscope initially followed by retinal photo)
- Test urine for protein
- Test blood for renal function (creatinine and eGFR)
- Check general condition of the feet, peripheral pulses and sensation
- Review cardiovascular risk factors
- Introduce self-monitoring and injection techniques if insulin is required
- Review dietary knowledge

- **Progress.** This patient was managed with lifestyle changes and Metformin, initially 500 mg daily. He will undertake surgery when his HbA1c is <7% (53 mmol/mol).

Management for surgery

Non-insulin-treated patients should stop medication 2 days before the procedure. Patients with mild hyperglycaemia (fasting blood glucose < 8 mmol/L) can be treated as non-diabetic. Those with higher levels are treated with soluble insulin prior to the procedure/surgery, and with glucose, insulin and potassium infusion during and after the procedure (p. 426). Be careful of hypoglycaemia due to the additive effect of medications taken previously. Postoperatively, patients should return to their normal management regimen when they begin eating and drinking.

Who needs insulin perioperatively?

- All patients who usually use insulin
- All acute surgical emergencies (type 1 and type 2 diabetes)
- All patients undergoing major surgery (type 1 and type 2 diabetes).

In other words, all diabetic patients should receive insulin except type 2 diabetic subjects undergoing minor surgery. For patients on insulin, give the usual evening and/or night-time insulin and commence glucose and insulin as above at 06:00.

URGENT SURGERY IN PATIENTS WITH DIABETES

Surgery requires patients to fast for several hours. In addition, a general anaesthetic and surgery themselves produce significant stresses on an individual. The hormonal response to stress involves a significant rise in counter-regulatory hormones to insulin, in particular cortisol and adrenaline. For this reason, patients with diabetes undergoing surgery will require an increased dose of insulin despite their fasting state. Long-acting hypoglycaemic agents must be stopped the night before surgery because hypoglycaemia might otherwise occur. In case of an emergency operation where the patient has taken a long-acting insulin, an infusion of 10% glucose can be used (usually with potassium), together with a controlled infusion of insulin.

The procedure for **insulin-treated patients** is simple:

Patients whose diabetic control is poor and when surgery is not an emergency should have their diabetic control reassessed and therapy adjusted with HbA1c < 8.5% (70 mmol/mol), if possible preoperatively.

Preoperative glucose levels should be in the range of 7–11 mmol/L.

The patient's usual insulin is given the night before the operation and, whenever possible, diabetic patients should be first on the morning procedure/operating list.

An infusion of glucose, insulin and potassium is given during the procedure/surgery. The insulin can be mixed into the glucose solution or administered separately by syringe pump. A standard combination is 16 U of soluble insulin with 10 mmol of KCl in 1 L of 5–10% glucose, infused at 125 mL/hour. The insulin dose is adjusted:

- Blood glucose < 4 mmol/L – 8 U/L
- Blood glucose 4–15 mmol/L – 16 U/L
- Blood glucose 15–20 mmol/L – 32 U/L.

Postoperatively, the infusion is maintained until the patient is able to eat. Other fluids needed in the perioperative period must be given through a separate IV line and must not interrupt the glucose/insulin/potassium infusion. Glucose levels are checked every 2–4 hours and potassium levels are monitored. The amount of insulin and potassium in each infusion bag is adjusted either upwards or downwards according to the results of regular monitoring of the blood glucose and serum potassium concentrations.

The same approach is used in the emergency situation, with the exception that a separate variable-rate insulin infusion may be needed to bring blood glucose under control before surgery.

DIABETIC FOOT

Case history

The chiropodist in the diabetic clinic asks you to review an 84-year-old woman who is complaining of severe pain in her big toe. She had attempted to cut a toe-nail a week ago and the toe had become painful and infected. She is known to have type 2 diabetes for which she takes glibenclamide 10 mg daily. She does not have regular supervision of her diabetes.

On examination she has a 2-cm ulcer on the medial side of her big toe with swelling and erythema.

Remember

- Many foot problems are avoidable. Older diabetic patients must be taught good foot care and should not cut their own toe-nails
- Diabetic foot problems can occur in patients with type 1 and type 2 diabetes.

What further points would be helpful in the history?

- Is there a previous history of foot problems?
- Does she regularly inspect and wash her feet? Is she careful about buying shoes of the correct size?
- How good is her sight?
- Does she live alone? Does she have any help?
- Is there any suggestion of peripheral vascular disease, e.g. intermittent claudication?
- Is there any suggestion of peripheral sensory problems? Does she complain of numbness or burning in her feet?

Remember

50% of patients have no previous history of neuropathy or peripheral vascular disease.

What particular points do you look for on examination?

- Inspect the lesion. Take a swab for culture.
- Look for signs of neuropathy:
 - Dry skin
 - Evidence of sensory loss to pin-prick/light touch/vibration
 - Check ankle jerks – absent knee and ankle jerks and sensory loss indicate a neuropathy.

- Look for signs of vascular insufficiency:
 - Check peripheral pulses
 - Are the toes cold?

Pathogenesis of foot ulcers

- Most ulcers occur as a result of trauma
- Neuropathy causes:
 - Reduced sensitivity
 - Altered proprioception with 'high pressure' on parts of foot
 - Autonomic dysfunction leading to dry skin with cracks and fissures.
- Peripheral vascular disease:
 - Very common
 - Leads to ischaemic ulcers (pure ischaemic ulcers in 10%). 90% of ulcers are due to neuropathy alone or a combination of neuropathy and ischaemia.

Information

Diabetes in India

- 50 million people with diabetes mellitus
- Foot problems are very common: these are due to neuropathic and infective causes rather than vascular

Management

- Admit the patient to a medical assessment unit.
- Take swabs for microbiology.
- Arrange an urgent X-ray to look for foreign bodies, gas and osteomyelitis.
- Early effective antibiotic treatment is essential:
 - Use broad-spectrum antibiotic cover until cultures are available, e.g. flucloxacillin, amoxicillin and metronidazole
 - Discuss with microbiologist.
- Control the diabetes with insulin until foot healed, when oral treatment can be restarted.
- Establish the presence of other diabetic complications (see above).
- Ask diabetic team to fully assess her and arrange for future follow-up care.

Information

Meggitt-Wagner classification of diabetic foot ulcers

- Grade 0: high-risk foot with no ulcers
- Grade 1: superficial ulcer
- Grade 2: deeper ulcer infection/cellulitis. No bone involvement
- Grade 3: osteomyelitis and foot ulceration
- Grade 4: localised gangrene (toes, forefoot or heel)
- Grade 5: gangrene of entire foot.

- **Progress.** This woman was admitted to MAU and seen by the Tissue Viability Nurse for daily dressings of her foot ulcer. The inflammation settled and she was discharged after 6 days with full nursing care at her own home. She was continued on glibenclamide and metformin.

Further reading

Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes – a review. *Diabet Med* 2010; **27**: 4–14.

DIABETES IN PREGNANCY

Case history (1)

You are asked to see a 28-year-old woman who is 18 weeks pregnant and has been found to have a blood glucose of 10 mmol/L. She is asymptomatic and gives no history of diabetes.

- **Diagnosis.** Gestational diabetes.

How should this patient be managed?

Meticulous glycaemic control is of paramount importance in pregnancy. The patient should initially be taught to monitor her blood glucose levels and be advised on lifestyle changes, including diet. Blood glucose levels should be measured 1 h after each meal. If blood glucoses are below 7 mmol/L, then insulin is not required. Oral hypoglycaemic agents are avoided in pregnancy because they cross the placental barrier (although there is evidence that glibenclamide is safe), so that if glucose levels are above 7 mmol/L, insulin therapy is required. High levels of glucose are associated with risk of neonatal macrosomia, fetal death and postnatal hypoglycaemia. Thus the patient should be commenced on soluble insulin with each meal and a long-acting insulin at night if glucose is not controlled to < 7 mmol/L.

Information

- Normal subjects have lower blood glucose during pregnancy
- Thresholds vary between diabetic units but a fasting glucose > 6 mmol/L or a random/post-prandial glucose > 7.8 mmol/L is an indication for home blood glucose monitoring
- Diet should be healthy but not restricted
- Have a low threshold to start insulin

- **Progress.** This patient required insulin therapy, which was continued until she delivered at normal term.

Case history (2)

You are called to the labour ward to see a patient who is on insulin and in labour. She has been on soluble insulin 12 units three times daily and Isophane insulin 18 units last thing at night, with very good control of her blood sugar. She is now in labour and is nil by mouth.

Immediate management of this patient?

An infusion of 5% glucose containing 10 mmol of KCl and 16 units of insulin in 1 litre is commenced at an initial rate of 125 mL/hour.

The dose of insulin is adjusted with hourly glucose assessment (see p. 426), with a target blood glucose of 4–9 mmol/L. The infusion is maintained until the patient is able to eat and drink.

It is essential to determine whether the patient had type 1 diabetes before pregnancy (in which case insulin should never be stopped) or whether she has gestational diabetes, when insulin therapy can be stopped after delivery. The placental hormones cause insulin resistance and, after the third stage of labour, gestational diabetes can disappear.

- **Progress.** This mother has type 1 diabetes, so she was commenced on her pre-pregnancy dose of insulin when she started eating. Intravenous insulin must be continued until 4 h after the first dose of subcutaneous insulin. She is followed up at her doctor's diabetic clinic.

CUSHING'S SYNDROME

Cortisol is the principal endogenous glucocorticoid secreted from the adrenal glands; the amount controlled by the level of plasma ACTH.

Cushing's syndrome is due to excess glucocorticoids due to the causes shown in the Information box, of which exogenous corticosteroid administration is the commonest.

Patients have undiagnosed Cushing's syndrome for some time, and present due to metabolic decompensation either due to hypokalaemia (which can be severe) or hyperglycaemia and resultant dehydration.

Other complications follow, including secondary infection, bruising and bleeding, uncontrollable hypertension and osteoporotic fractures (Fig. 14.2).

Information

Causes (percentages in brackets refer to incidence of primary cause)

- Excess corticosteroid administration
- Pituitary-dependent Cushing's disease (85%)
- Adrenal adenoma (10%)
- Ectopic ACTH production (5%)

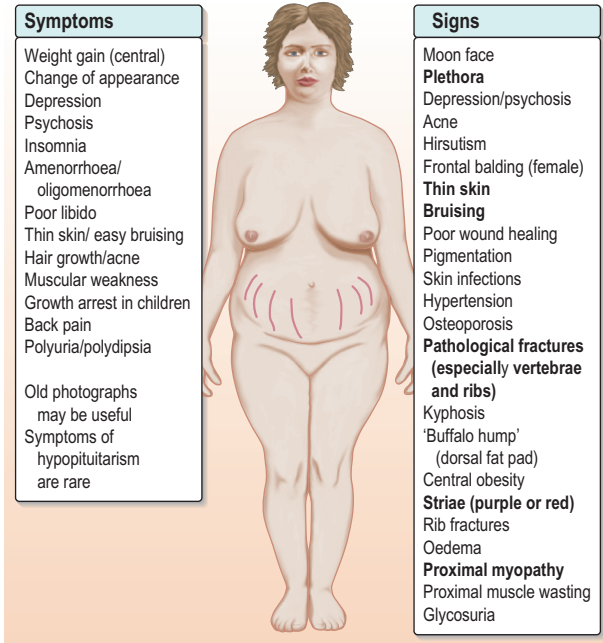


Figure 14.2 Symptoms and signs of Cushing's syndrome. The bold type indicates the signs of most value in discriminating Cushing's syndrome from simple obesity and hirsutism.

Case history

A 55-year-old woman presents with a 2-year history of atypical depression and 3 weeks of confusion, altered behaviour and an inability to climb stairs due to muscular weakness. Her weight has increased marginally but she has lost muscle bulk from the arms and legs.

On examination she was obese, plethoric with a moon face and buffalo hump. Her skin was thin with multiple striae over breasts, abdomen and thighs.

• **Diagnosis.** Cushing's syndrome.

She was dehydrated and was found to have glycosuria with a blood glucose of 30 mmol/L.

Arterial blood gases reveal:

- pH 7.60
- pO₂ 12.0 kPa
- pCO₂ 5.4 kPa.

This patient has a metabolic alkalosis due to chronic hypokalaemia found in Cushing's. Electrolytes came back from the laboratory, confirming your suspicions:

- Na⁺ 145 mmol/L
- K⁺ 2.5 mmol/L
- Urea 15.0 mmol/L
- Creatinine 120 µmol/L
- Bicarb 37 mmol/L
- Glucose 27 mmol/L.

How would you manage this patient?

The hypokalaemia and hyperglycaemia need prompt treatment. Total body potassium is likely to be extremely low, and as potassium is replaced, the initial effect will be to reduce the bicarbonate rather than to increase the extracellular (serum) potassium.

- Start potassium replacement both orally and intravenously (not more than 20 mmol in any 3 h) to provide at least 200 mmol per day.
- Rehydrate the patient with 0.9% saline + potassium chloride (40 mmol/L) added to each bag (see p. 426) with 2-hourly K⁺ monitoring.
- Start an intravenous infusion of insulin at 4 units per hour. This might exacerbate the fall in serum potassium.
- After 48 hours the lady was rehydrated with a serum K⁺ of 4.5 mmol/L.
- **Confirm the diagnosis of Cushing's syndrome.**
 - Collect 24-h urine for urinary free cortisol (normal < 700 nmoles in 24 hours)
 - Measure midnight cortisol (normal < 50 nmol/L).
 - 8-h low-dose dexamethasone suppression (0.5 mg 6-hourly for 48 h at 09:00, 15:00, 21:00, 03:00 followed by 09:00 cortisol).
 - **Progress.** Cushing's is confirmed and the patient is referred for specialist investigation. These investigations will include determination of ACTH dependence, pituitary and adrenal CT scanning and localisation procedures.

HYPERTHYROIDISM

Case history (1)

A 65-year-old woman is brought to A&E with acute breathlessness and cough with frothy blood tinged sputum.

On examination she had profuse sweating with rapid severe breathlessness. She has atrial fibrillation and auscultation reveals wheezes and crackles throughout the chest. Your diagnosis of **pulmonary oedema** is confirmed by the chest X-ray showing bilateral perihilar shadowing and Kerley B lines of interstitial oedema.

ECG shows fast AF 160/min but no evidence of cardiac ischaemia or other abnormality.

What should you do?

- Admit the patient to HDU and start treatment of acute heart failure, oxygen, IV furosemide 50 mg and vasodilation therapy glyceryl trinitrate infusion 100–200 µg min.
- She responds well but still has fast AF.
- **Urgent.** Thyroid function tests reveal a free T4 of 45 pmol/L (NR 9.0–23) with a suppressed TSH.
 - **Diagnosis.** Hyperthyroidism

Treatment

- Control the heart rate using beta blockers (propranolol 40 mg every 8 h) and digoxin if required.
- Avoid amiodarone as this will potentially interfere with investigation and management.
- Anti-coagulate the patient (heparin and warfarin).
- Start anti-thyroid medication, e.g. carbimazole 40 mg daily.
- Determine the cause of the hyperthyroidism (see below).

Beta adrenoreceptors are sensitised to normal circulating catecholamines by high levels of thyroxine and beta blockade is useful in achieving symptom control in hyperthyroidism, and is also helpful in treating high-output heart failure and achieving rate control. Propranolol is used in high doses (40 mg every 8 h) because, being lipid soluble, it crosses the blood-brain barrier.

Remember

- TSH is invariably suppressed in hyperthyroidism (except for the exceptionally rare TSH-secreting pituitary adenoma)
- Hyperthyroidism often presents in the elderly with atrial fibrillation and few other features.

Investigations

- Thyroid anti-microsomal autoantibodies and anti-thyroglobulin antibodies (in the serum): positive in up to 90% of patients with Graves' disease
- Thyroid technetium scan to distinguish a 'hot nodule' (focal uptake) from Graves' disease (uniform uptake) and from viral thyroiditis (zero uptake)

- **Progress.** This lady was confirmed as having Graves' disease. She was followed up for her hyperthyroidism with reduction of her carbimazole dosage. A cardiologist advised her to stay on digoxin and warfarin and she remained in AF at 6 months.

Further reading

Brent GA. Graves' disease. *NEJM* 2008; **358**: 2594–2605.

Case history (2)

A 75-year-old woman is referred with weight loss, general malaise and apathy.

Clinical examination is unremarkable except for a mild tachycardia of 100 bpm.

Routine investigations (remembering to include thyroid function tests) (Table 14.8), have now been telephoned by the biochemist with the following results:

- fT_4 : 56 pmol/L (NR: 9–23 pmol/L)
- TSH < 0.1 mU/L (NR: 0.3–5.5 mU/L)

Elderly patients can have atypical presenting features of hyperthyroidism, which may be dominated by weight loss, apathy and fatigue.

Remember

Weight loss without obvious cause always requires a TSH measurement.

Information

Hyperthyroidism in the elderly

- Weight loss
- Atrial fibrillation
- Lethargy
- Proximal myopathy

Table 14.8 Characteristics of thyroid function tests in common thyroid disorders (the clinically most informative tests in each situation are shown in bold)

	TSH (0.3–3.5 mU/L)	Free T₄ (10–25 pmol/L)	Free T₃ (3.5–7.5 pmol/L)
Thyrotoxicosis	Suppressed (<0.05 mU/L)	Increased	Increased
Primary hypothyroidism	Increased (>10 mU/L)	Low/low-normal	Normal or low
TSH deficiency	Low-normal or subnormal	Low/low-normal	Normal or low
T₃ toxicosis	Suppressed (<0.05 mU/L)	Normal	Increased
Compensated euthyroidism	Slightly increased (5–10 mU/L)	Normal	Normal

Causes of hyperthyroidism

Common causes

- Graves' disease
- Multinodular goitre
- Toxic solitary nodule
- Viral thyroiditis
- Amiodarone induced.

Rare causes

- TSH-secreting pituitary adenoma
- Choriocarcinoma
- Factitious (self-medication).

Tests in patients with goitres

- **Thyroid function tests** – TSH plus free T₄ or T₃.
- **Thyroid antibodies** – to exclude auto-immune aetiology.
- **Ultrasound.** Ultrasound with high resolution is a sensitive method for delineating nodules and can demonstrate whether they are cystic or solid. In addition, a multinodular goitre may be demonstrated when only a single nodule is palpable. Unfortunately, even cystic lesions can be malignant and thyroid tumours may arise within a multinodular goitre; therefore fine-needle aspiration (see below) is often required and performed under ultrasound control at the same time as the scan.
- **Fine-needle aspiration (FNA).** In patients with a solitary nodule or a dominant nodule in a multinodular goitre, there is a 5% chance of malignancy; in view of this, FNA should be performed. This can be done in the outpatient clinic. Cytology in expert hands can usually differentiate the suspicious or definitely malignant nodule.
- FNA reduces the necessity for surgery, but there is a 5% false-negative rate which must be borne in mind (and the patient appropriately counselled). Continued observation is required when an isolated thyroid nodule is assumed to be benign without excision.
- **Thyroid scan** (99^m technetium) can be useful to distinguish between functioning (hot) or non-functioning (cold) nodules. A hot nodule is only rarely malignant; however, a cold nodule is malignant in only 10% of cases and FNA has largely replaced 99^m technetium scans in the diagnosis of thyroid nodules.

Drug treatment in hyperthyroidism

- Rapid symptomatic treatment (if necessary): propranolol 40–80 mg 8-hourly
- Control thyroid overactivity:
 - Carbimazole 40 mg once daily *or*
 - Propylthiouracil (PTU) 200 mg × 3 daily.

The latter two drugs inhibit the formation of thyroid hormones (Fig. 14.3). Carbimazole and PTU will induce hypothyroidism after 4–8 weeks at these doses and treatment should either be titrated down to a maintenance level (e.g. carbimazole 10 mg daily) or thyroxine added back at a dose of 100–150 µg in a 'block and replace' regimen. Patients are typically treated for 6–18 months with anti-thyroid drugs. All patients commencing anti-thyroid drugs should be warned about possible rashes, which are common and usually self-limiting without discontinuation, and severe sore throats or mouth ulcers, which may indicate a dangerous fall in neutrophils.

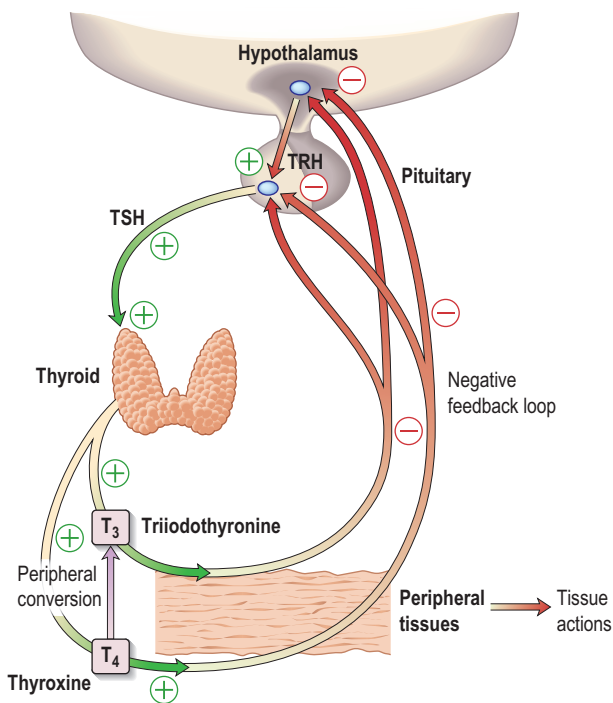


Figure 14.3 The hypothalamic-pituitary-thyroid axis. Pituitary TSH is secreted in response to hypothalamic TRH and stimulates secretion of T_4 and T_3 from the thyroid. T_4 and T_3 have actions in peripheral tissues and exert negative feedback on pituitary and hypothalamus.

Treatment with radioiodine is frequently employed if patients relapse after medical treatment but may also be used as primary treatment, particularly in multinodular goitres or toxic adenoma. Surgery is reserved for large goitres or for patient preference after relapse.

Remember

Agranulocytosis occurs in 1 : 1000 patients on anti-thyroid drugs. All patients prescribed anti-thyroid drugs should be warned to report severe mouth ulcers or sore throats immediately, and should have an urgent full blood count if symptoms are experienced.

Information

Investigation of a solitary nodule

- All solitary nodules > 1 cm should be evaluated, as should 'dominant' nodules in nodular goitres
- Fine-needle aspiration cytology is the first-line investigation to identify a papillary carcinoma or follicular neoplasm
- Ultrasound is used to diagnose multinodular goitre
- Isotope scanning might identify a toxic 'hot' solitary nodule; these are almost always benign

- **Progress.** This patient was treated with carbimazole and at 3 months was euthyroid.

Case history (3)

You have been telephoned by a doctor who has received the results of some thyroid function tests (TFTs) on one of his patients. The blood test report showed a high free T4: 45 pmol/L (10–25 normal range) with a suppressed TSH (< 0.1 mU/L). On further questioning it transpires that the test was performed in a patient who was unwell with a painful neck. You recommend a thyroid technetium uptake scan which shows minimal uptake, and arrange for the patient to come to outpatients in 2 weeks.

When you see the patient he is better but still clinically hyperthyroid and repeat TFTs are as follows: free T4 7 pmol/L; TSH 25 mU/L.

This patient is now biochemically hypothyroid, although the initial biochemistry demonstrated hyperthyroidism.

This presentation is strongly suggestive of **viral thyroiditis (de Quervain's)**. Thyroid hormones are released in the early stage (when the patient is thyrotoxic) and patients typically become biochemically, and later clinically, hypothyroid. The tissue effects of high levels of thyroxine last longer than their serum levels and symptoms often lag behind the biochemical changes.

- **Progress.** Viral thyroiditis does not usually require treatment; hypothyroidism is often transient, although a short course of thyroxine (3–6 months) should be used if high TSH persists. Autoantibodies might be positive because of the viral damage and do not necessarily predict long-term thyroid dysfunction. Thyroid function tests at 6–12 months were normal in this patient.

Features of viral (de Quervain's) thyroiditis

- Neck discomfort or pain on swallowing and a short course of prednisolone is used if pain is severe
- History of viral illness

- Hyperthyroidism (usually 1–3 weeks followed by hypothyroidism), followed by resolution
- Disparity between clinical features and biochemistry
- High ESR
- Reduced uptake on technetium uptake scan
- Weakly positive anti-thyroid antibodies.

Case history (4)

A 42-year-old female was brought to A&E as an emergency with a 24-hour history of vomiting, diarrhoea and two seizures. She had become confused and was now very drowsy.

She was accompanied by her partner who explains that she has been unwell for 6 months with a thyroid problem, for which she takes tablets. Following a severe cold 7 days ago he thinks that she has stopped her therapy.

On examination she has a GCS of 8 with the following findings.

- Tachycardia > 145 beats per minute, ? atrial fibrillation
- Hyperpyrexia > 41°C
- Heart failure
- Jaundice
- Psychosis.

Patients who have two or more of the above have a high mortality. Symptoms can also include vomiting, diarrhoea, seizures and coma.

Thyroid storm

This is defined as being present in a patient with hyperthyroidism biochemically and any two of the above features. It is a rare medical emergency because thyrotoxicosis is now easy to diagnose biochemically and can be treated earlier than formerly.

It can be precipitated by thyroid surgery, the administration of radioiodine, the withdrawal of or non-compliance with anti-thyroid medication and by acute illness.

Treatment

- Cool the patient with tepid sponging and a fan. Do not use aspirin, which is contraindicated in thyroid storm (it displaces thyroxine from its binding globulin and increases the free T₄).
- Beta blockers (propranolol 5 mg IV then 40–80 mg 8-hourly orally) unless contraindicated by asthma (*Note:* heart failure is not a contraindication to beta blockers).
- Fluid replacement: this needs careful assessment with central venous monitoring. Heart failure will rapidly come under control once the patient's heart rate is lowered.
- Hydrocortisone 100 mg IV 6-hourly. This blocks T₄ to T₃ conversion.
- Propylthiouracil 250 mg 4-hourly.
- Potassium iodide 60 mg 8-hourly as iodine blocks thyroxine synthesis and release. This should be given at least 1 h after the propylthiouracil, which blocks iodine incorporation, but not uptake.

- **Progress.** This woman responded to her emergency treatment and was referred back to the Endocrine team who have now recommended radioactive thyroid treatment.

AMIODARONE AND THYROID FUNCTION

Case history

A 45-year-old patient presents in A&E with increased breathlessness over the last few days. On direct questioning she says that she has been losing weight (8 kg) for 4 months. She gave a past history of heart problems, for which she is under the care of a cardiologist. She is unsure of the exact problem but says that she does take tablets for an irregular pulse that she has brought with her. She is on amiodarone and also takes warfarin and a diuretic.

On examination she has an irregular pulse 120/min, a raised JVP with crackles at both bases.

You diagnose **mild heart failure with atrial fibrillation** which is confirmed by ECG.

Treatment

You increase her diuretic to furosemide 80 mg daily and start her on enalapril at a small initial dose of 2.5 mg daily.

- **On post-take ward round:** Your consultant is pleased with your summary of the woman's condition and your initial management. He asks you about the weight loss, which you have noted but so far have no explanation for.

Fortunately you have done many blood tests, including thyroid function tests, the results of which are now available. These show a free T4 30.7 pmol/L and a TSH < 0.1 mU/L. How should you proceed?

- Confirm how long the patient has been on amiodarone and check the clinical record to establish whether there are any previous TFT results, particularly those before amiodarone therapy was commenced.
- Amiodarone can cause hypo- or hyperthyroidism. In patients who have nodular thyroid disease the synthesis of thyroxine may be autonomous and is limited only by iodine availability: thyrotoxicosis may be precipitated. In others, the Wolff-Chaikoff effect may result in hypothyroidism. Amiodarone also blocks T4 to T3 conversion, causing a high T4 and normal T3.
- Examine the patient for clinical evidence of hyperthyroidism.
- The patient is clinically, as well as biochemically thyrotoxic, so start carbimazole 40 mg daily and ask the patient's cardiologist to discontinue amiodarone and use other therapy for her atrial fibrillation. Amiodarone-induced thyrotoxicosis can require high doses of carbimazole and sometimes prednisolone is helpful in controlling the condition. Because amiodarone contains large amounts of iodine, radioiodine cannot be used.

Information

Amiodarone contains a substantial amount of iodine and has a half-life of about a month. Thus amiodarone behaves like slow-release iodine.

TFTs on amiodarone:

- Normal
- High fT4 normal TSH due to reduced conversion: monitor
- Subclinical thyrotoxicosis, i.e. suppressed TSH: change therapy
- Clinical thyrotoxicosis: change treatment and control overactivity
- Hypothyroidism: titrate thyroxine very gradually starting at 25 µg daily

Information

Wolff and Chaikoff first noted that excessive iodine suppresses thyroid function and causes short-term atrophy of the thyroid gland. Surgeons use this effect by administration of potassium iodide for 10 days before surgery. This is also why potassium iodide is used in thyroid storm.

- **Progress.** Cardiologists agreed that this patient should stop amiodarone and start verapamil. They said that two attempts at DC conversion had failed in the past and DC was unlikely to be successful now. The patient became euthyroid after 3 months carbimazole therapy.

HYPOTHYROIDISM

Case history

A 42-year-old woman is seen in the Well Women's Clinic because she is having irregular periods which are sometimes very heavy. She thinks she has become menopausal and wonders about HRT. A more detailed history reveals that she has general malaise, weight gain (5 kg in 6 months), constipation and a hoarse voice.

On examination she is overweight at 68 kg (BMI 30). There is no palpable goitre but she does have swollen, non-pitting oedema of her legs and slow relaxation of her ankle jerks.

Diagnosis: Hypothyroidism.

Investigations show a raised TSH (30 µg/L) and free T4 of 4.2 pmol/L, confirming hypothyroidism. Interpretation of thyroid function tests is shown in [Figure 14.4](#).

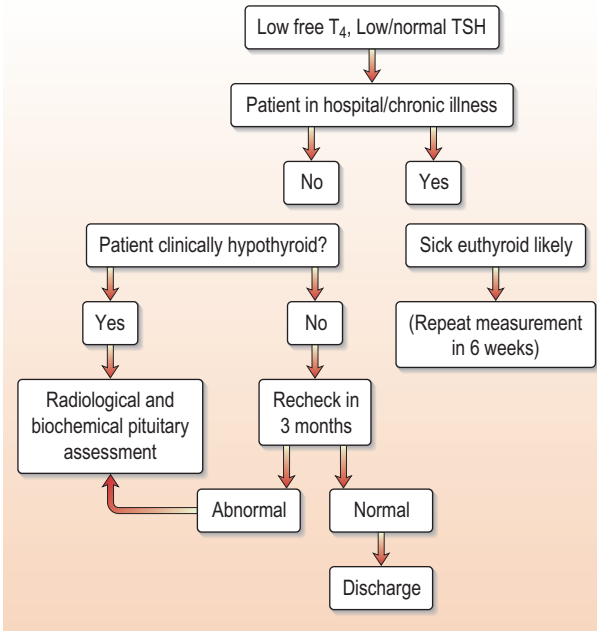


Figure 14.4 Interpretation of thyroid function tests.

Hypothyroidism is now diagnosed by a multitude of practitioners:

- Lipid clinic: cause of hypercholesterolaemia
- Psychiatrists: organic psychosis or depression
- Neurologists: ataxia
- ENT surgeons: dysphonia or deafness
- Cardiologists: during follow-up on amiodarone treatment
- Dermatologists: dry skin or hair
- Gynaecologists: menorrhagia, oligo- or amenorrhoea, infertility
- Geriatricians: screening test
- Diabetologists: screening test in diabetes.

In primary hypothyroidism, the TSH will *always* be elevated and often very high.

Adult-onset primary hypothyroidism is usually due to autoimmune disease, unless:

- Amiodarone treatment
- Previous thyroid surgery
- Previous radioiodine treatment
- Viral or post-partum thyroiditis.

Treatment

The patient, who is otherwise fit and not at risk of ischaemic heart disease, is started on 100 µg levothyroxine daily.

And then ...?

It takes about 6 weeks for a steady state to be reached. Aim to increase the levothyroxine dose in 25 µg increments every 6 weeks until the TSH is within or just below the normal range (3–3.5 mU/L). Occasionally, patients require only 50–75 µg daily although usually 100–150 µg daily is required. Think about associated autoimmune diseases:

- Vitamin B₁₂ deficiency
- Myasthenia gravis
- Addison's disease
- Coeliac disease
- Other organ specific autoimmune diseases.

If the patient had angina, be very careful indeed. Many clinicians start at 25 µg per day (or even alternate days) and increase every 4–6 weeks. With hypothyroidism or when attempting thyroxine replacement with unstable angina, treat the heart disease first.

What is compensated hypothyroidism?

Early in the course of hypothyroidism the TSH is elevated (4–20 mU/L) but T4 and T3 are normal. Opinion differs as to the need for treatment. Most endocrinologists replace with levothyroxine:

- If autoantibodies are present in high titre
- If the patient has typical symptoms of hypothyroidism
- In the presence of a high cholesterol
- TSH > 10 mU/L.
 - *Progress.* The patient made a complete recovery on levothyroxine therapy and did not require HRT.

ADDISON'S DISEASE

Case history

A 35-year-old teacher has been under the care of a gynaecologist whom she consulted for amenorrhoea and menopausal symptoms. She has been increasingly tired and has lost weight over a 6-month period. She presents acutely to A&E with a 2-day history of vomiting and postural hypotension.

On examination she has a dull, slightly grey/brown pigmentation easily seen on her palmar creases. Her blood pressure is 80/60 with a postural drop.

Electrolytes:

- Sodium: 127 mmol/L
- Potassium: 5.2 mmol/L
- Urea: 16 mmol/L
- Creatinine: 140 µmol/L.

The clinical presentation and electrolytes indicate **adrenal insufficiency**. Treatment with glucocorticoids (e.g. hydrocortisone) and IV 0.9% saline is life-saving in this situation and should be started immediately after a blood sample is taken for plasma cortisol/ACTH measurements.

Adrenal insufficiency presents gradually – over months – but also, as in this case, with acute haemodynamic collapse, often precipitated by infection, trauma or surgery. Crises can also occur in patients with known Addison's disease during relatively trivial episodes such as a viral infection; for this reason patients are advised to increase (typically double) the dose of hydrocortisone during illness.

Patients who are on long-term steroids for inflammatory conditions such as asthma also have pituitary adrenal suppression but do not develop the same pattern of electrolyte disturbance and rarely become so unwell because they have preserved mineralocorticoid (i.e. aldosterone) secretion.

Clinical findings in Addison's disease

Acute

- Hypotension (may be severe or postural)
- Nausea and vomiting
- Diarrhoea
- Hyponatraemia and hyperkalaemia
- Metabolic acidosis
- Hypercalcaemia
- Mild elevation of TSH.

Chronic

- Weight loss and anorexia
- Fatigue
- Generalised weakness
- Hyperpigmentation
- Arthralgia and myalgia
- Depression and apathy and confusion.

Information

Common causes of adrenal failure

- Primary:
 - Autoimmune: often associated with other autoimmune disease (e.g. type 1 diabetes mellitus, hypothyroidism, premature ovarian failure)
 - Tuberculous adrenalitis: consider in immigrant populations/developing countries
 - Drugs (e.g. ketoconazole, metyrapone)
- Secondary (i.e. due to ACTH deficiency):
 - Long-term glucocorticoid therapy (oral, inhaled, topical or intranasal steroids)
 - Hypopituitarism

Immediate management of this patient

General

- IV 0.9% saline
- Correct hypoglycaemia with 5% glucose
- Identify and treat a precipitating cause.

Specific

- Take samples for cortisol and ACTH.
- Hydrocortisone (100 mg IM); the intramuscular route gives sustained plasma levels.
- Continue hydrocortisone 50–100 mg IV/IM \times 4 daily.

Further investigations

- FBC (anaemia, normochromic normocytic)
- Glucose (hypoglycaemia)
- Serum calcium (might be high)
- ABGs (acidosis)
- CXR (TB, carcinoma)
- Short tetracosactide test (see Information box) if necessary to confirm diagnosis
- Pituitary MRI if hypopituitarism suspected

The initial cortisol in this woman was < 100 nmol/L so that Addison's disease is confirmed. In a less clear cut case, use a tetracosactide test.

- **Progress.** Once the patient had recovered and is eating and drinking, hydrocortisone replacement was rapidly tapered to 20 mg daily, given as 10 mg (06:00) + 5 mg (12:00) + 5 mg (18:00) to try and mimic the physiological circadian rhythm. Fludrocortisone was commenced at 100 μ g daily.

Information**Short ACTH (Tetracosactide) test**

- Omit morning and previous evening dose of hydrocortisone
- Take baseline blood sample for cortisol and ACTH
- Administer tetracosactrin 250 μ g IM or IV
- Take further blood samples for cortisol at 30 and 60 min
- 30 minute cortisol < 500 nmol/L is abnormal (500–600 nmol/L is borderline)

Further reading

Arit W, Allolio B. Adrenal insufficiency. *Lancet* 2003; **362**: 1881–1894.

PATIENTS ON STEROIDS FOR SURGERY**Case history**

A 50-year-old woman who is known to have chronic asthma and who has been on oral prednisolone between 10 mg and 40 mg for at least the last 10 years is admitted for a right hemicolectomy for a caecal carcinoma. Her asthma has been difficult to control on inhalers alone and she finds that her asthma worsens whenever her dose of oral prednisolone is reduced to 10 mg, which she is on at present.

How should the patient's steroids be continued following surgery?

Patients who have been on prednisolone for more than 3 months are likely to have a suppressed pituitary–adrenal axis (Fig. 14.5). Adrenal mineralocorticoid production will be normal, so that the risks of a typical Addisonian crisis are small, but nevertheless this patient will not be able to mount the normal cortisol response to surgery. Glucocorticoid replacement should be given as follows:

- At induction: hydrocortisone 100 mg IM; then
- 50–100 mg IM or IV for 3 days.

An intravenous infusion of hydrocortisone (25–100 mg over 24 h, i.e. 1–4 mg per hour) should be given to all patients who will have a prolonged period NBM or who are on ITU. The pharmacokinetics of hydrocortisone are such that such a continuous infusion of 4 mg will achieve a steady-state plasma cortisol level of > 500 nmol/L, similar to patients on ITU with normal adrenals. A serum cortisol sample after 12 h of infusion can be used to titrate the hydrocortisone infusion down to achieve a cortisol level of 500–750 nmol/L. Hydrocortisone 100 mg every 6 h when given IM will also achieve a similar concentration of cortisol.

Note: Oral hydrocortisone has a greater bioavailability than intravenous hydrocortisone.

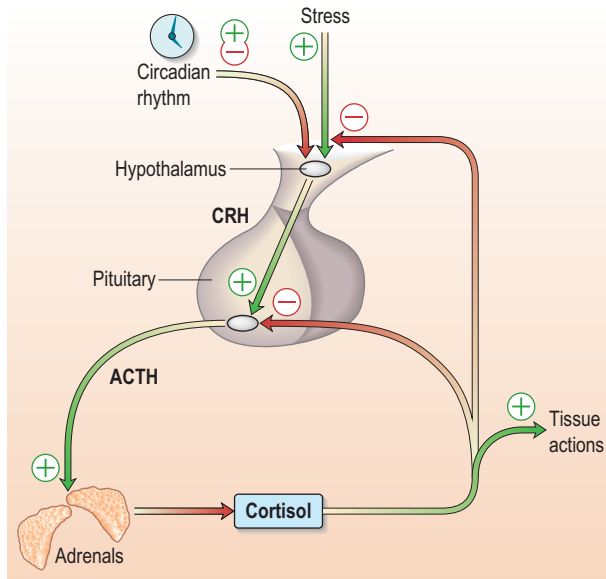


Figure 14.5 Control of the hypothalamic-pituitary-adrenal axis. Pituitary ACTH is secreted in response to hypothalamic CRH (corticotrophin-releasing hormone) triggered by circadian rhythm, stress and other factors, and stimulates secretion of cortisol from the adrenal. Cortisol has multiple actions in peripheral tissues and exerts negative feedback on pituitary and hypothalamus.

Information

Once-daily steroids are used in pharmacological doses to treat inflammatory conditions. Such treatment is not appropriate for hydrocortisone replacement in patients with Addison's disease, patients who have congenital adrenal hyperplasia (who might not be able to synthesise any adrenal steroids) or following adrenalectomy, when patients are at risk of true Addisonian crises. These patients need twice-daily treatment.

- **Progress.** This patient's postoperative period was prolonged due to her asthma and she spent 48 hours in ITU. She eventually made a good recovery but is continuing to need oral steroids.

HYPERCALCAEMIA

Case history (1)

A 56-year-old female patient who has been found to have fibroids has been admitted for a hysterectomy. She has treated hypertension but no other known illness, and no symptoms other than menorrhagia. A routine biochemical screen has revealed a corrected calcium of 2.75 mmol/l (NR 2.20–2.60 mmol/L).

Information

An incidental finding of a raised serum calcium is a common presentation of hypercalcaemia and should be evaluated.

What is the appropriate management of this case with mild hypercalcaemia?

Mild to moderate hypercalcaemia: corrected calcium < 3.00 mmol/L.

- Ensure breast examination and CXR are reviewed
- Ensure adequate hydration preoperatively
- Continue IV 0.9% saline (1 L 8-hourly) postoperatively until patient is drinking freely
- U&Es and calcium postoperatively
- Follow-up with full investigation.

Investigations

- Urea, electrolytes and eGFR
- Serum PTH
- ESR
- Serum electrophoresis and immunofixation for paraprotein

Investigations (continued)

- Serum free light chain assay
- 24-h urine collection for calcium estimation
- CXR
- TFTs
- Serum angiotensin converting enzyme levels (for sarcoidosis)

Clinical features of moderate/severe hypercalcaemia

- Malaise, tiredness, fatigue
- Anorexia and weight loss
- Thirst and polyuria
- Non-specific musculoskeletal symptoms
- Renal calculus (stones)
- Osteoporosis ('bones')
- Abdominal pain ('groans')
- Confusion ('psychic moans').

Causes**Information**

- Primary hyperparathyroidism is the most common cause of mild-moderate hypercalcaemia
- Malignancy accounts for 50% of severe hypercalcaemia and is usually apparent with physical examination + CXR and breast examination

PTH dependent

- Primary hyperparathyroidism (the most common cause of mild hypercalcaemia)
- Tertiary hyperparathyroidism (in the context of chronic kidney disease)
- Familial hypocalciuric hypercalcaemia (slightly raised PTH).

PTH independent

- Myeloma
- Solid tumours: breast, bronchus, kidney, lymphoma
- Vitamin D excess (especially the 1 alpha analogues of vitamin D)
- Sarcoidosis
- Thyrotoxicosis
- Glucocorticoid insufficiency.

Biochemical features of primary hyperparathyroidism

- Elevated PTH in the presence of hypercalcaemia. High normal PTH with hypercalcaemia also suggests hyperparathyroidism because any other cause of hypercalcaemia should suppress the PTH.
- Elevated or high/normal 24-h urinary calcium excretion (normal: 2-8 mmol/24 h).

- Low bicarbonate 15–20 mmol/L (PTH excess causes a mild renal tubular acidosis).
- Moderately elevated ESR.
- Normochromic anaemia.

Familial hypocalciuric hypercalcaemia (FHH) is a benign, familial, autosomal dominant condition caused by a mutation of the calcium-sensing receptor in the kidney and parathyroid gland. It is not associated with renal calculi and is asymptomatic. It can be difficult to distinguish from asymptomatic primary hyperparathyroidism. A low urinary calcium suggests the diagnosis, which is confirmed by examining family members.

Treatment of primary hyperparathyroidism

Patients who are symptomatic or who have complications should all be referred for parathyroid surgery, whatever the serum calcium level.

Most authorities suggest that the majority of asymptomatic patients should also be treated surgically because they are at risk of developing complications, and should certainly be referred for specialist opinion.

- **Progress.** This patient had an uneventful postoperative recovery following her hysterectomy but did not want to consider any further surgery unless it becomes absolutely necessary. She is being followed with regular serum calcium levels.

SEVERE HYPERCALCAEMIA

Case history

A 72-year-old woman is referred with a diagnosis of 'recurrent hyperparathyroidism'. She had a past history of primary hyperparathyroidism treated surgically 10 years previously and had been maintained on a low dose of oral calcium.

Three months prior to admission she had become generally unwell, weak and lethargic. She reported weight loss of 5 kg. The GP had performed blood tests: corrected calcium 3.5 mmol/L; urea 16 mmol/L; creatinine 150 μ mol/L. Renal function was previously normal. The patient arrived dehydrated and vomiting. She was found to have a fungating breast carcinoma, which she had kept secret.

- Recurrence of hyperparathyroidism after surgical cure is unusual and suggests a familial cause of hyperparathyroidism (e.g. multiple endocrine neoplasia) or an alternative cause, e.g. breast cancer.
- Hypercalcaemia causes dehydration by creating a secondary type of nephrogenic diabetes insipidus. As calcium clearance is itself dependent on GFR, hypercalcaemia can rapidly decompensate in the presence of fluid depletion.

Management of this patient's severe hypercalcaemia

Information

Severe hypercalcaemia is defined as: corrected calcium > 3.5 mmol/L or > 3.0 with evidence of dehydration.

- Aggressive rehydration with 0.9% saline 4–6 L over 24 h.
 - Central venous pressure monitoring is usually necessary. This is usually sufficient to bring calcium down to 3.0 mmol/L.
 - Bisphosphonate: treatment of choice for hypercalcaemia of malignancies or of undiagnosed cause. 60–90 mg infusion of disodium pamidronate via a cannula in a large vein causes normalisation of serum calcium in 80% of patients after 48 to 72 h.
- Other treatments:
- Glucocorticoids (e.g. prednisolone 60 mg daily is used in sarcoidosis or vitamin D toxicity).
 - In life-threatening hypercalcaemia, haemodialysis may be necessary.
 - **Progress.** This patient's calcium level remained within the normal range for 2 weeks. She was referred to the Oncology Department for treatment of the breast cancer and was started on an oral bisphosphonate as skeletal secondaries were demonstrated.

HYPOCALCAEMIA

Case history

Three days after a total thyroidectomy, a 32-year-old patient develops tingling and numbness around the mouth and in the extremities. She has become emotionally labile.

On examination tapping the facial nerve (Chvostek's sign) her upper lip twitches. A serum calcium is 1.82 mmol/L corrected. How do you proceed?

Management

- The patient's parathyroid glands might have been inadvertently removed. Before the plasma calcium result is available, an urgent assessment of the patient must be made to determine the severity.

Clinical features of hypocalcaemia

- Abnormal neurological sensations and neuromuscular excitability
- Numbness around the mouth and paraesthesia of the distal limbs
- Hyper-reflexia
- Carpal and pedal spasms
- Tetany contractions (may include laryngospasm)
- Generalised seizures

- Chvostek's sign is elicited by tapping the facial nerve just anterior to the ear, causing ipsilateral contraction of the facial muscles (positive in 10% of normals).
- Trousseau's sign is elicited by inflating a blood pressure cuff for 3 min at the level of systolic blood pressure. This causes mild ischaemia, unmasks latent neuromuscular hyperexcitability and carpal spasm is observed.
- ECG: prolonged QT interval.

Information

Causes of tetany

In the presence of alkalosis:

- Hyperventilation
 - Excess antacid therapy
 - Persistent vomiting
 - Hypochloraemic alkalosis, e.g. primary hyperaldosteronism
- In the presence of hypocalcaemia: see below

How do you assess severity?

The symptoms and signs described above are a much better guide to prognosis than the absolute value of the plasma calcium. In the presence of a low calcium (corrected calcium less than 2.0 mmol/L), any of the above features should be taken as evidence that urgent treatment is required.

Treatment of this patient (Table 14.9)

- Administer 10 mL calcium gluconate (10 mL of 10% calcium gluconate (2.20 mmol)) before the plasma calcium result is back.
- Hypocalcaemia is usually transient.

Investigations

- Plasma calcium (and albumin) and phosphate
- Plasma magnesium
- U&Es
- Plasma PTH level (low in hypoparathyroidism, high in vitamin D deficiency)
- Vitamin D level
- Skull XR (intracranial calcification of chronic hypocalcaemia)

Causes of hypocalcaemia

- Hypoparathyroidism (primary, secondary or most commonly post-surgical)
- Renal failure (associated hyperphosphataemia)
- Vitamin D deficiency (giving rickets and osteomalacia)
- Pseudo-hypoparathyroidism (resistance to PTH)

Table 14.9 Management of symptomatic hypocalcaemia

Severity of hypocalcaemia	Recommended action
Emergency Spontaneous tetany, laryngospasm, seizures	Give 10 mL calcium gluconate 10% over 5 min IV, then proceed as below
Acute severe hypocalcaemia Frequent spasms/distressing symptoms and corrected calcium < 2.00 mmol/L or	Calcium infusion: calcium gluconate at 15 mg/kg IV over 4 h in 1 L 0.9% saline. This is equivalent to [(weight in kg) × 1.7] mL of 10% calcium gluconate
Mild symptoms and corrected calcium of < 1.90 mmol/L	ECG monitoring is essential for patients with arrhythmias Check magnesium level and correct if low
Acute mild hypocalcaemia Mild symptoms with calcium 1.90–2.20 mmol/L	Oral calcium supplements Calcium carbonate (600 mg Ca ²⁺ daily) 1–2 tablets twice or three times daily. Preferably between meals to increase availability of calcium for intestinal absorption. If hypocalcaemia associated with insufficient vitamin D give calcium carbonate with colecalciferol 1 tablet twice or three times daily (Ca ²⁺ 600 mg)
Chronic hypocalcaemia Symptoms frequently mild unless accompanied by osteomalacia	Oral calcium supplements (as above) If due to dietary vitamin D deficiency use oral calcium as above With hypoparathyroidism: either primary, secondary or persisting following thyroid/parathyroid surgery: add alfacalcidol 1 µg daily. This medication requires careful monitoring and usually endocrine follow-up

- Severe magnesium deficiency (causes both reduced PTH secretion and resistance to PTH action)
- Acute pancreatitis
- Rhabdomyolysis.

How do you manage symptomatic hypocalcaemia?

The aim of acute management is not to return the calcium to normal but to ameliorate the acute manifestations of hypocalcaemia (Table 14.9).

- **Progress.** This patient's serum calcium was normal on the 4th post-operative day and she made an uneventful recovery.

Information

Administration of alfacalcidol (0.5–1.0 µg), together with oral calcium gluconate, is used for chronic hypoparathyroidism with regular calcium monitoring.

PHAECHROMOCYTOMA (CATECHOLAMINE CRISIS)

Phaeochromocytomas are rare catecholamine-producing tumours derived from neuroendocrine cells, usually involving the adrenal glands (90%) or elsewhere in the sympathetic chain (paragangliomas).

Case history

Three hours after a surgical procedure for colonic malignancy, a 62-year-old woman becomes hypertensive with tachycardia, inappropriate lactic acidosis and hyperglycaemia. When you review the notes you discover that she has a 3-cm adrenal mass seen on a CT scan preoperatively, which was felt to be an incidental finding by the surgical team. On further questioning, you determine that she has had a history of paroxysmal palpitations, flushing, sweating attacks and headaches for years.

This history and CT findings would be compatible with a phaeochromocytoma.

Phaeochromocytoma is known as the 10% tumour (see Information box). It can be diagnosed during routine screening of hypertensive patients (found in only 0.1% of hypertensive subjects), the investigation of unusual episodes or cardiac events of uncertain aetiology. Phaeochromocytomas are usually associated with hypertension, 'attacks' and/or headache. They secrete adrenaline or noradrenaline (Fig. 14.6).

Information

Phaeochromocytoma – the 10% tumour

- 10% are bilateral
- 10% are extra-adrenal, usually around the sympathetic chain, when they are known as paragangliomas
- 10% are malignant

How do these tumours present?

Symptoms and signs of catecholamine excess include:

- Hypertension (sustained or paroxysmal)
- Anxiety attacks
- Palpitations and tachycardia
- Cold extremities

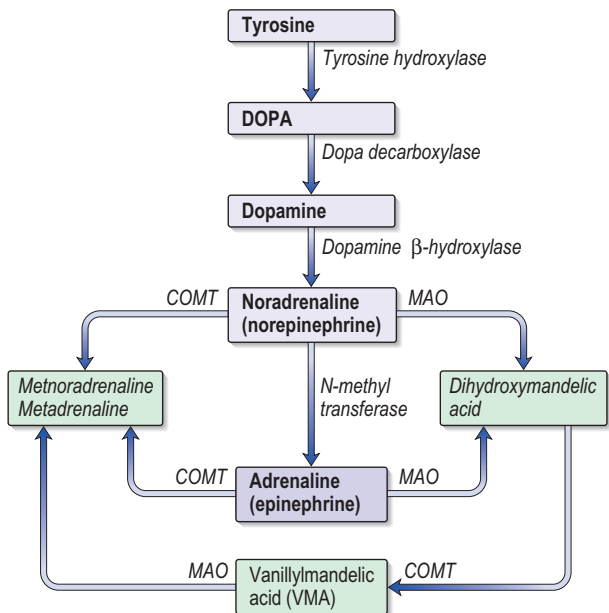


Figure 14.6 The synthesis and metabolism of catecholamines. DOPA, dihydroxyphenylalanine; COMT, catechol-O-methyl transferase; MAO, monoamine oxidase.

- Cold sweats, tremor, pallor
- Cardiac arrhythmias including atrial and ventricular fibrillation
- Hypertensive crises may be precipitated by intercurrent illness, surgery, or drugs (e.g. beta blockers, tricyclic anti-depressants, metoclopramide and naloxone)
- Pulmonary oedema with normal LV function
- Unexplained lactic acidosis
- Apparent type 2 diabetes.

Associations

A family history is vital, particularly in young patients, and might reveal the following autosomal dominant conditions:

- Neurofibromatosis type I (neurofibromata, café au lait spots, Lisch nodules (iris hamartomas) and axillary freckling)
- von Hippel-Lindau disease (cerebellar haemangioblastomas, retinal haemangiomas and renal cell carcinoma)
- Multiple endocrine neoplasia type 2 (medullary thyroid carcinoma and hyperparathyroidism)
- Hereditary paraganglioma syndromes (phaeochromocytoma, carotid body tumour).

Diagnostic tests include

- U&Es: potassium often low, urea may be high if dehydrated
- Glucose: hyperglycaemia.
- Urinary catecholamines (adrenaline, noradrenaline and dopamine) are measured by most laboratories. Two sets of normal 24-h urinary catecholamines make a pheochromocytoma very unlikely.
- Plasma (heparinised) catecholamines (adrenaline, noradrenaline and dopamine) are specific but not sensitive tests. The blood must be taken directly to the lab for centrifugation.
- MRI/CT scan of the adrenals should be delayed until biochemical diagnosis but are useful in localising the lesion.
- MIBG scan: MIBG (¹³¹I-metaiodobenzylguanidine) is taken up selectively by adrenal tissue and is useful for localisation of tumour, particularly in extra-adrenal sites.

How would you manage this case?

- Adequate fluid replacement with 1 L 0.9% saline initially over 1 hour, then 1 L 8-hourly, usually with CVP monitoring.
- Initiate oral alpha blockade: phenoxybenzamine 10 mg × 3 daily increasing gradually to 40 mg × 3 daily.
- When the blood pressure is controlled with phenoxybenzamine and a reflex tachycardia occurs, add propranolol 10–40 mg × 3 daily. Do not use Labetalol.
- Surgery: hypotension commonly occurs intra-operatively when the tumour is removed, and this should be managed with blood, plasma expanders and inotropes as required. Inotropes should be used only when the patient is appropriately fluid replete. Expansion of intravascular volume 12 h before surgery significantly reduces the frequency and severity of postoperative hypotension.
- In emergency (hypertensive crisis) intravenous phentolamine (1–5 mg) should be used, but great care should be taken to adequately rehydrate the patient in order to prevent severe hypotension.
 - *Progress.* This patient improved with α and β blockade and her blood pressure stabilised. She was referred to the Endocrine Department who, after further investigations, recommended surgical removal of the tumour.

HYPOPITUITARISM

Pathophysiology

Deficiency of hypothalamic releasing hormones or of pituitary trophic hormones can be selective or multiple. Thus isolated deficiencies of GH, LH/FSH, ACTH, TSH and vasopressin are all seen, some cases of which are genetic and congenital and others sporadic and autoimmune or idiopathic in nature.

Multiple deficiencies usually result from tumour growth or other destructive lesions. There is generally a progressive loss of anterior pituitary function. GH and gonadotrophins are usually first affected. Hyperprolactinaemia, rather than prolactin deficiency, occurs relatively early because of loss of tonic inhibitory control by dopamine. TSH and ACTH are usually last to be affected.

Case history

A 60-year-old man is admitted with a sudden onset of explosive headache and a left third nerve palsy. CT scan showed no evidence of an intracranial haemorrhage. An LP showed a mild lymphocytosis.

Viral meningitis is suspected but his recovery is slow. He is noted to have small testes and a hypogonadal appearance. Six weeks later he is readmitted with weight loss and a chest infection. Endocrine screening shows a low 09:00 serum cortisol and undetectable serum testosterone.

- **Diagnosis.** Hypopituitary coma and apoplexy.

Pituitary apoplexy occurs with infarction or haemorrhage into an undiagnosed pituitary tumour. It produces severe headache with sudden visual field defects or ocular palsy. Axial CT scan can miss pituitary apoplexy but MRI usually shows the tumour.

Features of pituitary apoplexy

Pituitary infarction can be silent. Apoplexy implies the presence of symptoms:

- Headache occurs in 75% of cases (may be sudden onset, very severe, or mild)
- Visual disturbance (compression of optic tract, usually causing bitemporal hemianopia)
- Ocular palsy present in 40% of cases: unilateral or bilateral
- Nausea/vomiting
- Meningism
- Hemiparesis.

Clinically, pituitary apoplexy can be very difficult to distinguish from subarachnoid haemorrhage, bacterial meningitis, mid-brain infarction (basilar artery occlusion) and cavernous sinus thrombosis.

Initial investigation

An MRI of the pituitary reveals a tumour mass. *Note:* MRI will often reveal a pituitary tumour although it cannot distinguish between recent and old haemorrhage (CT might help).

A single clotted blood sample should be taken to measure cortisol, thyroid function, prolactin, growth hormone, testosterone (in men) and the gonadotrophin hormones.

Assessment of severity

The course of pituitary apoplexy is variable. Headache and mild visual disturbance can develop slowly and persist for several weeks. In the acute form, apoplexy might cause optic nerve compression, haemodynamic instability, coma and is potentially fatal. Neurosurgical advice should always be sought. Residual endocrine disturbance invariably occurs. Panhypopituitarism is the usual result. Table 14.10 shows the replacement therapy that is required.

Table 14.10 Replacement therapy for hypopituitarism

Axis	Usual replacement therapies
Adrenal	Hydrocortisone 15–40 mg daily (starting dose 10 mg on rising/5 mg lunchtime/5 mg evening) (Normally no need for mineralocorticoid replacement)
Thyroid	Levothyroxine 100–150 mcg daily
Gonadal Male Female	Testosterone IM, orally, transdermally or implant Cyclical oestrogen/progestogen orally or as patch
Fertility	HCG plus FSH (purified or recombinant) or pulsatile GnRH to produce testicular development, spermatogenesis or ovulation
Growth	Recombinant human growth hormone used routinely to achieve normal growth in children Also advocated for replacement therapy in adults where growth hormone has effects on muscle mass and well-being
Thirst	Desmopressin 10–20 mcg 1–3 times daily by nasal spray or orally 100–200 mcg 3 times daily Carbamazepine, thiazides and chlorpropamide are very occasionally used in mild diabetes insipidus
Breast (prolactin inhibition)	Dopamine agonist (e.g. cabergoline 500 mcg weekly)

FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; HCG, human chorionic gonadotrophin.

Information

- Neurosurgical decompression via a trans-sphenoidal route is the definitive treatment for pituitary apoplexy
- Obtundation and visual deterioration are absolute indications for neurosurgery
- Patients without confusion or visual disturbance generally do well without surgery

Management of this patient's acute hypopituitarism

- Diagnostic samples for cortisol, TFTs, prolactin (single plain venous sample).
- Hydrocortisone 100 mg (preferably IM) should be administered when the diagnosis is suspected.
- Administer glucose if the patient is hypoglycaemic.
- Investigate and treat his chest infection.

How do patients with hypopituitarism present?

- Patients present at times of stress (e.g. following a general anaesthetic) with hypoglycaemia due to the combination of a lack of GH, cortisol and thyroxine, all of which have a counter-regulatory effect on insulin.
- Post-partum infarction of the gland occurs following post-partum haemorrhage and vascular collapse during a difficult delivery (Sheehan's syndrome). This diagnosis should be suspected with failure to lactate, amenorrhoea and general ill-health post-partum.
- Other features of hypopituitarism are non-specific and include tiredness, weakness, loss of body hair and loss of libido (sexual interest) and features of hypothyroidism.
- Note that patients with ACTH deficiency have no postural blood pressure drop and normal electrolytes, as adrenal mineralocorticoids (aldosterone) are unaffected.

Assessment of severity

The degree of hypopituitarism bears little relationship to the clinical state of the patient. In the absence of stress, patients with severe hypopituitarism might have few complaints. Examination of the testes in males might reveal small testes and women can demonstrate either amenorrhoea or inappropriately low post-menopausal gonadotrophins. Patients with mild hypopituitarism might become profoundly unwell at times of stress, such as during an intercurrent infection.

Causes

- Destruction of the pituitary gland by primary or metastatic tumour
- Ischaemic necrosis after post-partum haemorrhage
- Pituitary apoplexy
- Post-pituitary surgery or radiotherapy
- Primary empty sella syndrome.

Investigations of anterior pituitary function

- Baseline blood samples must be taken for cortisol, free thyroid hormone levels, testosterone LH, FSH, prolactin and growth hormone levels.
- Dynamic investigation of pituitary function can be deferred and the patient should be treated expectantly with hydrocortisone (e.g. 10 mg \times 2 daily once stable).
- Imaging using CT with fine cuts through the pituitary or MRI is indicated to find any space-occupying lesion.
 - **Progress.** This patient's hypopituitarism improved without surgery and at 3 months his serum hormone levels were normal. He was evaluated further for possible treatment of his pituitary adenoma.

DIABETES INSIPIDUS

Transient diabetes insipidus (DI) often occurs following pituitary surgery because of vasopressin deficiency, and can also occur acutely following head injury. Consider DI if asked to see a patient with polyuria and polydipsia who has normal blood glucose. DI is also a cause of hypernatraemia.

Case history

You are called to see a patient who had a trans-sphenoidal hypophysectomy the day before for a non-functioning pituitary adenoma. He has made a good recovery from surgery but now complains of severe thirst and is passing large volumes of dilute urine. Results of his investigations:

- Na⁺: 146
- K⁺: 4.0
- Urea: 4.7
- Creatinine: 90
- Urine SG (dipstick): 1.001.

This patient probably has transient diabetes insipidus.

How would you manage this patient?

- Ensure adequate access to water or commence IV glucose 5% and 0.18% saline to match urine output if the patient cannot drink enough.
- Make sure an accurate fluid balance chart is being maintained.
- If urine output > 200 mL/hour for 2 consecutive hours, check plasma and urine osmolality.
- DI is confirmed by the presence of a high plasma osmolality (> 290) in the presence of an inappropriately low urine osmolality (< 500 mOsmol/kg).
- Start desmopressin: adult dose 0.5–1.0 µg SC stat followed by 10–40 µg × 3 daily as an intranasal spray.
- If the plasma osmolality is low the patient might be over-drinking due to a dry mouth, and a low urine osmolality is appropriate. In this circumstance, administration of desmopressin will cause a further fall in plasma osmolality and can be dangerous.

Other causes of diabetes insipidus

Diabetes insipidus is either cranial (CDI) or nephrogenic (NDI) due to the inability of ADH to act on the kidney (Table 14.11).

- **Progress.** This patient's DI was transient and he improved with IV fluids.

Table 14.11 Cranial and nephrogenic causes of diabetes insipidus

Cranial DI	Nephrogenic DI
Hypothalamic tumour	Drugs:
Basal skull fracture	diuretics
Neurosarcoidosis	lithium
(other hypothalamic disease)	Hypercalcaemia
Idiopathic	Hypokalaemia
Infection	Kidney disease e.g. renal tubular
Inflammatory	acidosis
	Idiopathic

SYNDROME OF INAPPROPRIATE ANTI-DIURETIC HORMONE (SIADH)

Inappropriate secretion of ADH results in retention of water and subsequent hyponatraemia. Mild symptoms of confusion, irritability and nausea occur as sodium levels fall below 125 mmol/L (125 meq/L); fitting and coma occur as the sodium falls below 115 mmol/L. A diagnosis of SIADH can only be made in a patient who is clinically normovolaemic with normal thyroid and adrenal function.

Case history

A 65-year-old smoker complained of a chronic cough and haemoptysis. A chest X-ray revealed a hilar mass. He was referred to the chest clinic for further investigation. Electrolytes: Na 118; K 4.4; U 3.3; Cr 100; glucose 4.9; measured plasma osmolality 255.

In view of the low plasma osmolality, a spot urine was also sent to the biochemistry department:

Urinary sodium 30 mmol/L; urinary osmolality 350 mOsm/kg.

This patient's urinary osmolality is high for his current plasma osmolality. Normally, the kidney can make urine as dilute as 100 mOsmol/kg (urine SG = 1.0001) or as concentrated as 1300 mOsmol/kg in a patient who is dehydrated (urine SG = 1.4000). The current urinary osmolality has to be interpreted with the knowledge of the current plasma osmolality.

This patient does indeed have **inappropriate ADH**. He was put on a 1-litre fluid restriction daily and commenced on demeclocycline.

Mild hypovolaemia is a potent stimulus for vasopressin (anti-diuretic hormone; ADH) release, and volume-depleted patients given hypotonic fluid will frequently become hyponatraemic. Assessment of volume status and recent fluid charts is essential in assessing hyponatraemia.

Information

Syndrome of inappropriate anti-diuretic hormone (SIADH)

- Dilutional hyponatraemia due to excessive water retention
- Low plasma osmolality with higher 'inappropriate' urine osmolality
- Continued urinary sodium excretion > 30 mmol/L
- Absence of hypokalaemia (or hypotension)
- Normal renal, adrenal and thyroid function

How would it present?

Most commonly, patients with true SIADH present with incidentally discovered hyponatraemia. Alternatively, patients might present with a fit or episodes of confusion.

Causes

- Small-cell lung carcinoma (commonest)
- Drugs (e.g. carbamazepine, SSRIs)
- Pneumonia
- Tuberculosis
- Intracranial pathology
- Other neuroendocrine tumours.

What other causes of hyponatraemia should you think of?

It is essential that other causes of hyponatraemia (in particular diuretics) are excluded. The diagnosis of SIADH cannot be made in a patient who is on diuretics, although a patient might have SIADH and also be on diuretics. The differential diagnosis of hyponatraemia includes hypothyroidism, adrenal and renal insufficiency, and chronic states such as cirrhosis and CCF.

Investigation of hyponatraemia

- Take a drug history, e.g. diuretics, SSRIs or carbamazepine.
- U&Es and plasma osmolality: hyponatraemia will be seen.
- Urinary electrolytes and osmolality.
- The patient will have a low plasma osmolality (< 280) and an inappropriately concentrated urine (> 300).
- Free T4 and TSH to exclude hypothyroidism.
- Cortisol and short ACTH test (p. 445) to exclude Addison's disease.
- CXR and chest CT (TB, carcinoma).
- CT/MRI brain (exclude intracranial pathology).

Treatment

- Fluid restriction
- Demeclocycline.
 - *Progress.* On fluid restriction and demeclocycline, this patient's serum Na⁺ returned to normal levels. He was referred to the oncologists for management of his bronchial carcinoma.

DIPLOPIA

Diplopia (double vision) occurs when there is an acquired defect of movement of an eye (paralytic squint). It is maximal in the direction of action of the weak muscle.

Case history (1)

A 70-year-old man with type 2 diabetes presents with a 12-hour history of double vision. He is taking metformin and glibenclamide for his diabetes.

On examination there is ptosis in the left eye and the eye is deviated downwards and laterally (down and out) and fails to elevate or move medially (Fig. 15.1). The pupils both react normally. He is otherwise well. Random blood glucose is 11.5 mmol/L. HbA1c is 8% (64 mmol/mol).

The **diagnosis** is a *mononeuritis* (usually a pupil-sparing third nerve palsy), a complication of diabetes mellitus.

What immediate action would you take?

- Achieve better diabetic control.
 - Put a patch over the eye.
 - Reassure that recovery is likely (but not definite) over weeks.
- If no recovery, refer to a neurologist for MRI scan and investigation of causes of mononeuritis multiplex (see p. 471).

Information

- A *painless third nerve palsy with preserved pupil reactions* commonly occurs in the setting of diabetes due to nerve infarction.
- If there is headache, especially of sudden onset, a posterior communicating artery aneurysm compressing the third nerve in front of the midbrain is a likely cause. Such a lesion also commonly involves the parasympathetic pupillary constricting fibres so that the pupil is fixed and dilated. MR angiography is indicated in this situation (Fig. 15.2).

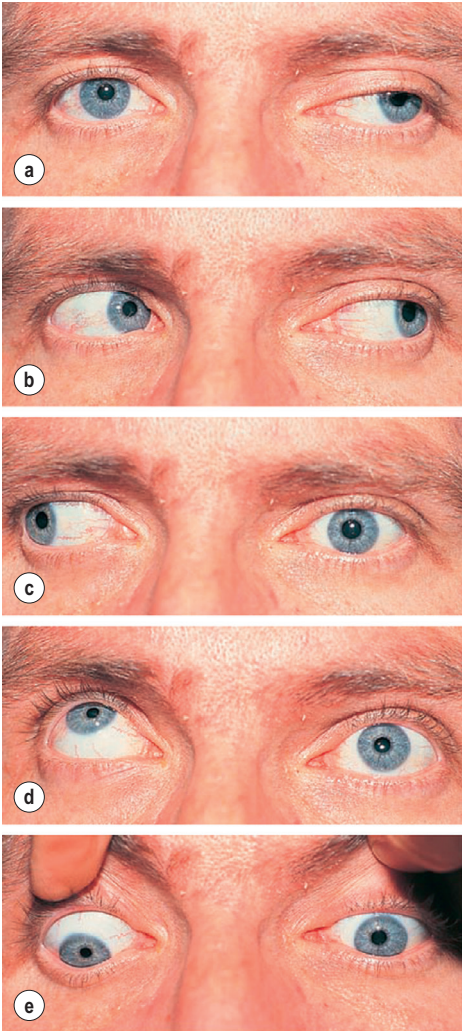


Figure 15.1 Partial left 3rd nerve palsy with mild ptosis in a man without diabetes. a) Large left pupil, b) normal left gaze, c) no adduction of left eye on right gaze, d) poor elevation, e) poor depression.

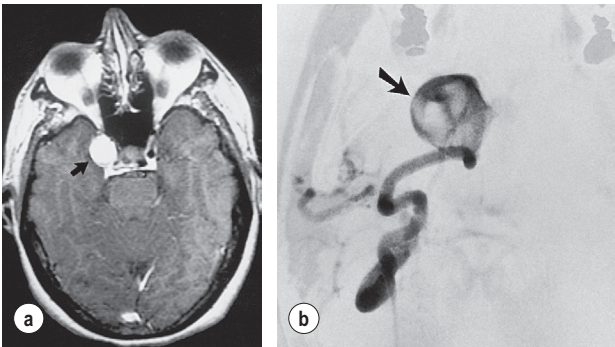


Figure 15.2 a) MRI showing left cavernous carotid aneurysm (arrow) b) MR angiogram showing an aneurysm (from Albert and Jakobiec's Principles and Practice of Ophthalmology. Saunders 2008 with permission).

- **Progress.** This woman's diplopia improved over the next 2 months.

Case history (2)

A 35-year-old woman presents with 3 months of intermittent double vision.

On examination there is mild restriction of upgaze and lateral gaze of the left eye, and mild restriction of upgaze of the right eye. There is mild bilateral ptosis. Further examination reveals fatiguability of the ptosis and of the eye movements.

A **clinical diagnosis** of **myasthenia gravis** was made.

What action would you take?

Confirm diagnosis of myasthenia by:

- Serum acetylcholine receptor antibodies (present in 40% of cases with eye involvement only with 100% specificity).
- Perform EMG studies, including the extra-ocular muscles.
- MRI of mediastinum to exclude thymoma.

This patient was diagnosed as having myasthenia gravis and was referred urgently to a neurologist. Myasthenia gravis is sometimes restricted to the ocular system and can present as a variable gaze palsy that is difficult to interpret in terms of individual muscles or cranial nerves. There is not always a history of fatiguability. Some of the many causes of diplopia are listed in Table 15.1.

Treatment

Treatment of myasthenia gravis includes oral anticholinesterases, e.g. neostigmine or pyridostigmine (dosage gradually increased), steroids, immunosuppression, and plasmapheresis. Restricted ocular myasthenia

Table 15.1 Causes of diplopia

Muscle/obstructive	Thyroid eye disease
	Orbital masses
	Orbital pseudotumour (ocular myositis)
	Myasthenia
	Latent squint (visible when tired)
Cranial nerves	Mass lesion in path of III, IV or VI nerves
	Mononeuritis multiplex
	False localising due to raised intracranial pressure
Central	Brainstem inflammation, demyelination, brainstem mass lesion, infarction, haemorrhage

carries a better prognosis, as swallowing and the respiratory muscles may be permanently spared.

Thymectomy may be necessary, even in patients without a thymoma.

This woman remains well on pyridostigmine at regular intervals through the day but in view of the high doses required (>360 mg) she was put on immunosuppressive therapy (azathioprine and steroids). She got side effects of abdominal colic from the pyridostigmine and this was helped by oral propantheline.

Further reading

Chaudhuri A, Behan PO. Myasthenic crisis. *QJM* 2009; **102**: 97–107.

Case history (3)

A 30-year-old, 27-weeks pregnant woman complains of 4 weeks of headache, nausea, brief one-second episodes of visual loss and horizontal double vision that is worse on distance gaze.

On examination she is found to have bilateral papilloedema (Fig. 15.3) and bilateral restriction of lateral gaze consistent with sixth nerve palsies.

What action would you take?

- MR or CT scan of head.

In this case the ventricles were normal and therefore it was safe to proceed to a lumbar puncture. The opening pressure was recorded at 30 cm (normal pressure < 25 cm). A volume of CSF (usually around 20 mL) should be removed, so as to approximately halve the opening pressure.

- **Diagnosis.** This woman has **idiopathic intracranial hypertension (IIH)**. This is most common in overweight females and rare in males.



Figure 15.3 Papilloedema.

Precipitating factors

- Pregnancy
- Weight gain
- Polycystic ovaries
- Tetracyclines
- Vitamin A excess (including retinoids)
- Steroids.

Management

Repeated lumbar puncture and removal of CSF, e.g. every 1–2 weeks, has been widely used but is probably not helpful. Drugs such as acetazolamide can be helpful. Treatment is directed primarily at preventing visual loss due to uncorrected papilloedema and secondly for relief of headache/diplopia. The visual fields must be checked formally at intervals by screen perimetry to monitor any enlargement of the blind spots. If repeat puncture is unsuccessful in this usually self-limiting condition, optic nerve fenestration or even ventriculoperitoneal shunting may be necessary.

Remember

- There are a number of secondary causes of raised intracranial pressure without dilated ventricles or other space-occupying lesion, e.g. venous sinus thrombosis and meningeal disease
- MRI/MR venography and examination of CSF constituents is therefore mandatory.

- *Progress.* This patient's condition improved post-partum.

LOSS OF VISION

Case history (1)

A 64-year-old man presents in the A&E with visual loss in the right eye for 3 hours. He had a previous episode several months earlier. He describes the loss as a horizontal screen descending over his vision. You are called by the A&E officer to give an opinion. When you arrive the visual loss has recovered.

What is the most likely diagnosis?

Temporary monocular visual loss with a horizontal defect in this age group is very likely to be **amaurosis fugax**. This is often caused by thromboembolism in the ophthalmic artery and is a symptom of carotid stenosis.

Investigation and management

See pp. 175 and 176.

What is the differential diagnosis?

Transient ischaemic attacks (TIAs) are usually diagnosed clinically. Other causes of visual loss are shown in Table 15.2.

Remember giant cell arteritis, which causes acute visual loss. It responds to steroids (see p. 182).

Abrupt and progressive visual loss over days is also seen in elderly hypertensives. There is often disc swelling and later disc pallor. This is due to an arteriopathy of the posterior ciliary artery resulting in ischaemia of the optic disc causing an anterior ischaemic optic neuropathy. Urgent management by a specialist is with heparin infusion and mannitol.

Table 15.2 Causes of acute or transient visual disturbance

Ophthalmological	Neurological
Glaucoma	Optic neuritis/demyelination
Amaurosis fugax	Compressive lesion of the optic nerve, chiasm, tract
Giant cell (temporal) arteritis	TIA/stroke of posterior cerebral circulation
Anterior ischaemic optic neuropathy	Migraine
Central retinal vessel occlusion	Occipital, temporal, parietal haemorrhage
Vitreous haemorrhage	Occipital, temporal, parietal space-occupying lesion
Retinal detachment	Temporal lobe epilepsy
Uveitis, keratitis	Raised intracranial pressure

- **Progress.** This patient's carotid doppler showed a 70% stenosis in the carotid artery and an internal carotid endarterectomy was performed. He has had no further episodes.

Case history (2)

A 24-year-old woman complains of several attacks of loss of vision, lasting up to 1 hour, in the right eye, accompanied by a left-sided pounding headache. Closer questioning reveals that the defect is in fact in the right visual field of both eyes.

Visual hemifield disturbance, sometimes with shimmering or jagged line scotomata, is a relatively common aura experienced by patients with **migraine**. Occasionally there is no headache.

If the symptoms are dramatic or atypical, or especially if there are any fixed symptoms or signs, an MRI scan should be performed to check for an underlying vascular lesion such as an arteriovenous malformation or underlying epileptogenic lesion, including occipital tumour.

Treatment

- **Paracetamol** 1 g, **aspirin** 900 mg (dispersible formulation) or an NSAID, e.g. **ibuprofen** 400–600 mg or **naproxen** 500 mg is given, as early as possible during an attack. Gastric emptying is reduced during the attack so dispersible formulations are preferred.
- Antiemetics (e.g. **metoclopramide** 10 mg or **domperidone** 10 mg).
- If these measures are ineffective, use a 5-hydroxytryptamine (5HT)_{1B/1D} serotonin receptor agonist (**triptan**). These drugs relieve both the pain and the nausea. Triptans should be avoided in patients with vascular disease or uncontrolled/severe hypertension. Triptans should be given at the onset of the headache (e.g. during the aura phase). There are several triptans available with a spectrum of efficacy, e.g.:
 - Sumatriptan 25–100 mg at onset of headache, repeat if necessary after at least 2 hours, max. 300 mg in 24 hours; SC 6 mg sumatriptan produces highest efficacy and most rapid response.
 - Zolmitriptan 2.5 mg at onset, repeat if only partial response after 2 hours; 5 mg also available.
 - Rizatriptan 10 mg at onset, repeat after 2 hours if only partial response.
 - Oro-dispersible formulations exist for some triptans but absorption is slower.
- If there is no response to an initial dose, do not persist with subsequent doses during the same attack. However, the drug may be effective in subsequent attacks.
 - **Progress.** This patient's headache improved with paracetamol and sumatriptan. On subsequent episodes of migraine she was able to self-administer sumatriptan, an anti-emetic and paracetamol at the onset of her headaches. With this regimen her migraine has been manageable.

Further reading

Loder E. Triptan Therapy in Migraine. *N Engl J Med* 2010; **363**: 63–70. 2010.

BELL'S PALSY

Case History

You are called to see a 45-year-old man who woke up this morning with a 'numb' left face, a droopy left eyelid and drooling from the left side of his mouth.

On examination, it is apparent that his 'numbness' represents left facial weakness in the upper and lower distributions. There is no sensory loss and no lesions of the skin around or inside the ear (Ramsey Hunt Syndrome).

An acute VII nerve lesion, **Bell's palsy** (Fig. 15.4) is usually due to a viral infection (often herpes simplex). It involves the VII facial nerve (motor only) with occasionally a loss of taste on the tongue and hyperacusis. There should be no sensory loss or other cranial nerve involvement.

Treatment is with steroids (60 mg prednisolone for a week) and tailing down over the subsequent 1–2 weeks, with an anti-viral, e.g. aciclovir given if diagnosed early. The patient should be reassured and the cornea protected if exposed. Sometimes recovery is incomplete and faulty reinnervation of the facial muscles or of the lacrimal gland may occur. Relapses are seen.

Bilateral or recurrent Bell's palsy, or one that shows no recovery after several weeks, should be investigated with an MRI scan, possibly CSF analysis, and investigations for causes of **mononeuritis multiplex**.

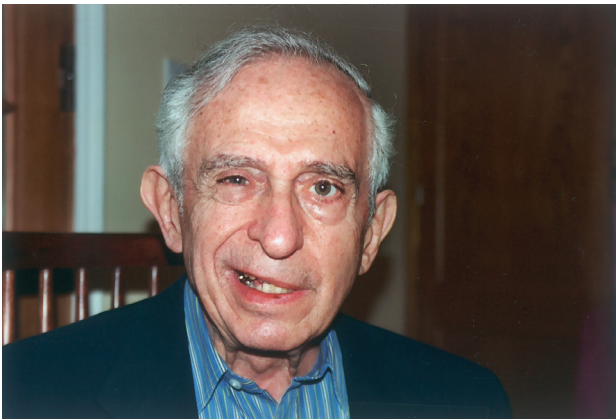


Figure 15.4 Bell's palsy.

Investigations

Mononeuritis multiplex

- FBC
- U&Es
- Blood glucose
- Serum autoantibodies
- Serum anti-cardiolipin antibodies
- Serum ANCA
- Treponemal serology
- *Borrelia* serology
- Serum and CSF angiotensin-converting enzyme
- Serum electrophoresis and Bence-Jones protein
- CXR

Note:

- Sarcoidosis should be suspected in cases of bilateral Bell's palsy.
- A rare condition causing bilateral Bell's palsy and tongue swelling with other features is Melkersson-Rosenthal syndrome.
- Progressive multiple cranial nerve palsies should lead to suspicion of malignant meningitis, or lymphomatous or carcinomatous infiltration.
 - **Progress.** This patient was treated with steroids and aciclovir and the palsy resolved over a few weeks. He has had no further recurrences.

Further reading

De Almeida JR, Al Khabori M, Guyatt GH et al. Combined corticosteroid and antiviral treatment for Bell palsy: a systematic review and meta-analysis. *JAMA* 2009; **302**: 985-993.

VERTIGO

Vertigo, the definite illusion of movement of the subject or surroundings, typically rotatory, indicates a disturbance of the vestibular nerve, brainstem or, very rarely cortical function. Deafness and tinnitus accompanying vertigo indicate involvement of the ear or cochlear nerve.

Case history (1)

An 85-year-old woman presented to A&E with a history of severe nausea, vomiting and dizziness, which started on waking one morning 2 weeks previously. She was confused and dehydrated. On rehydration she was able to give a clear history of true vertigo (the sensation of the environment spinning or rotating about her). The symptoms were precipitated by head movement, especially when she turned her head in bed.

On examination she has a normal eye movement. The rotational nystagmus in both eyes was brought on by sudden head movements (Hallpike's manoeuvre).

What is the likely diagnosis?

This history is typical of **vestibular neuronitis**, the aetiology of which is uncertain. It occurs at any age. Recovery generally takes place to a large extent over 2–3 weeks, although complete recovery might take several months. Cinnarizine and other vestibular suppressants give symptomatic relief but are best avoided in the long term.

Peripheral vestibular lesions are characterised by positional vertigo, i.e. influenced – often in a stereotyped way – by head movement. This is manifest in the Hallpike's test (Information box; Fig. 15.5), which characteristically reveals a rotational nystagmus.

Information

Hallpike's test

The patient is sat on a couch with her eyes open and facing the side of the lesion. The examiner swings the patient backwards so that she is supine and her head is below horizontal. Nystagmus following a latent interval of a few seconds is commonly noted if the test is positive.

A **central vestibular lesion** is sometimes also positional but generally fails to habituate (i.e. on Hallpike's testing, continued repetition of the same movement results in no reduction in the unpleasantness or in the nystagmus).

The definitive investigation to differentiate the two sites and to lateralise the lesion is by caloric tests.

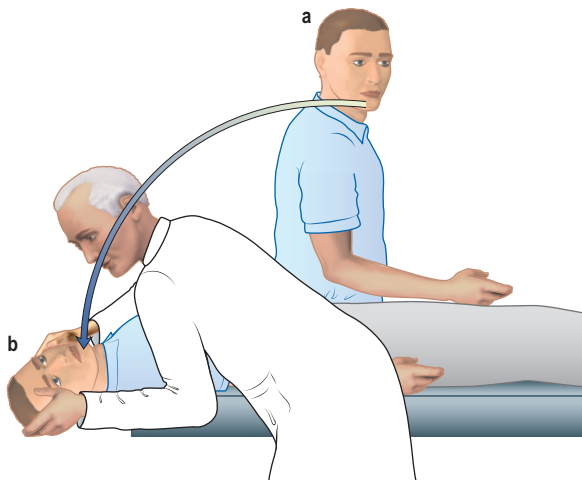


Figure 15.5 Hallpike manoeuvre for diagnosis of Benign paroxysmal positional vertigo.

Remember

- If there is a suspicion of a central lesion, an MRI scan should be performed
- Always check for associated deafness, tinnitus, cranial nerve lesions or cerebellar disturbance for early identification of a cerebellopontine angle lesion, most commonly an VIII nerve Schwannoma ('acoustic neuroma').

Main causes of vertigo

- Peripheral:
 - Vestibular neuronitis
 - Benign paroxysmal positional vertigo
 - Meniere's syndrome
 - Lesion of the VIII nerve, e.g. schwannoma
 - Inner ear infections, infiltrations.
- Central:
 - Brainstem infarction, inflammation or demyelination
 - Brainstem space-occupying lesion
 - Posterior circulation TIA
 - Migraine
 - Complex partial seizures.
 - **Progress.** This patient's vertigo settled after 5 days and has not recurred.

Case history (2)

A rather anxious woman presents to A&E with occasional, very brief blackouts and a long history of dizziness in crowds or when walking past fast-moving traffic. She prefers to avoid any sudden head movements, especially in certain directions and when turning in bed. Hallpike's test is positive.

What is the likely diagnosis?

Benign paroxysmal positional vertigo (BPPV). This is a relatively common disorder presenting with true vertigo, particularly on head movement. There are often vague 'vestibular hypersensitivity' symptoms, especially precipitated when there are conflicting visual inputs such as being stationary in a fast-moving visual field. Occasionally, the vertigo may be so sudden and dramatic as to present as a blackout.

Diagnosis

Largely clinical, although caloric testing may reveal mild dysfunction and MRI helps to exclude other conditions.

Management

Vestibular physiotherapy in the form of Cawthorne-Cooksey exercises (repetitive eye and head movements) and vestibular suppressants (e.g.

β -histine). In some cases the cause is said to relate to fragments of calcification in the semicircular canals; some specialists perform the Epley manoeuvre; a gentle manipulation and rotation of the head, in an attempt to dislodge these fragments away from the receptors. Some severe cases may be successfully treated by surgical section of the nerve to the ampulla of the posterior semicircular canal.

- **Progress.** The patient has vestibular physiotherapy and was taught to continue the exercises at home. She continues to have dizziness in crowds but is better.

Case history (3)

A 70-year-old man presents with sudden onset of vertigo, vomiting, gait unsteadiness and left facial numbness.

On examination there is coarse unidirectional nystagmus, reduced left corneal reflex, left Horner's syndrome, mild dysphagia and palatal deviation to the right, left-sided ataxia and impaired pin-prick on the right arm and leg.

This is a **partial left lateral medullary syndrome** due to a stroke in the territory of branches of the posterior or anterior inferior cerebellar arteries. The vertigo is usually not positional. Nystagmus of brainstem origin is often coarse, may be in any direction, often unidirectional and sometimes monocular.

Management

As for a stroke; see below.

STROKE

This is the sudden onset of focal neurological symptoms caused by interruption of the vascular supply to a region of the brain (ischaemic stroke) or intracerebral haemorrhage (haemorrhagic stroke). It is a common cause of mortality and physical disability.

Pathophysiology

Ischaemic stroke (infarction of central nervous tissue) results from cerebral infarction secondary to either arterial thromboembolism or emboli arising from the heart (e.g. in atrial fibrillation, mural thrombus after acute myocardial infarction, or rarely from vegetations in infective endocarditis).

Cerebral haemorrhage is often caused by microaneurysm rupture in small penetrating arteries in hypertensive patients. It can also occur by rupture of an aneurysm or arteriovenous malformation or by amyloid angiopathy in older patients. It accounts for ~15% of strokes.

Other causes of stroke in younger patients include arterial dissection, venous sinus thrombosis, thrombophilia, vasculitis and paradoxical embolisation through a patent foramen ovale.

Case history (1)

A 70-year-old man presents with a two and a half hour history of right-sided arm, leg and face weakness and loss of speech. He has no headache and is mildly confused. He has a history of ischaemic heart disease.

On examination he has a global dysphasia, full visual fields, upper motor neurone distribution right facial weakness and dense weakness (UMN distribution) of the right side with absent reflexes and an upgoing plantar response on that side. His pulse was regular.

A clinical diagnosis of **left middle cerebral artery ischaemic stroke** is made.

What immediate action would you take in this case (i.e. cerebral infarct)?

- Is thrombolysis to be considered? Yes. This stroke occurred less than 180 min ago, therefore immediate diffuse weighted **MRI** (more sensitive than CT) if available should be performed (Fig. 15.6). Unfortunately it was not available for this patient.
- CT will distinguish haemorrhage immediately but infarction cannot be seen early on (Fig. 15.6a).

An early CT scan is also useful in stroke to check for subarachnoid or intracerebral haemorrhage and to help exclude other conditions that may masquerade as stroke, such as tumour, cerebral abscess and cerebral venous sinus thrombosis.

In this patient the CT showed no evidence of haemorrhage, therefore **cerebral infarction** was likely.

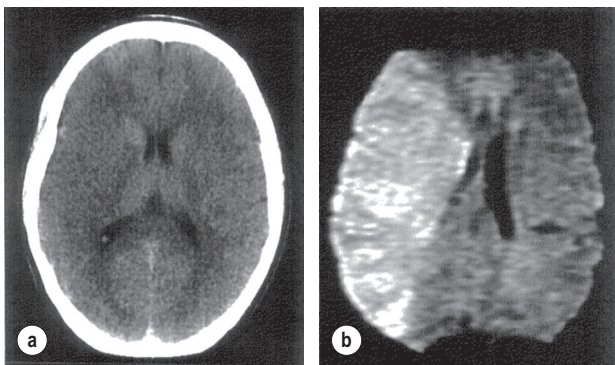


Figure 15.6 a) CT of a Middle cerebral infarct performed in the early stages showing subtle changes in right MCA territory. b) MRI of same region done at the same time as the CT showing the full extent of the damage. (Courtesy of Dr Paul Jarmon).

He was given IV tissue plasminogen activator (tPA) after ruling out contraindications and consenting the patient as soon as possible (MINUTES COUNT). Total dose 0.9 mg/kg; maximum 90 mg. Give 10% of total dose over 1 min and the remainder over 60 min by infusion (thrombolytic therapy is recommended by Cochrane reviews).

(If there had been a contraindication to the therapy or if thrombolysis is not available, he would have been given 300 mg aspirin.)

Remember

- If cerebral haemorrhage is shown on CT: do NOT give any therapy that might interfere with clotting, e.g. aspirin or heparin
- If posterior fossa haemorrhage: refer to neurosurgeons for possible emergency clot evacuation.

Other immediate action

- Give O₂ by mask.
- Do blood tests (Hb, WCC, U&Es, glucose, ESR).
- Admit to multidisciplinary hospital stroke unit.
- Check:
 - Blood pressure: do not over-correct systemic hypertension in acute phase
 - Swallowing: nil by mouth and IV fluids in any major stroke; assess properly by speech therapist
 - Asymptomatic aspiration is common, therefore early referral to physiotherapy and other support services
 - Treat for any concurrent infection, other illness or electrolyte disturbance.
- If there is evidence of cerebral oedema and risk of coning, give IV mannitol.

Further management

- Start aspirin 75 mg daily (24 hours after if tPA has been given).
- Dipyridamole slow release.
- Anti-coagulants if in atrial fibrillation.
- Serum cholesterol: if fasting > 3.5 mmol/L (not in acute situation), give atorvastatin 10 mg daily.
 - **Progress.** This patient did not make an early clinical improvement as can occur after thrombolytic therapy (37%) but by 3 months he was ambulant, with a minor neurological deficit, and had improved speech.

Further reading

Wechsler LR. Intravenous thrombolytic therapy for acute ischemic stroke. *N Engl J Med* 2011; **364**: 2138–2146.

Case history (2)

A 56-year-old man presents with weakness of the left hand and face lasting 3 hours and resolving gradually. He had a similar episode 3 months earlier with complete recovery. He is a type 2 diabetic and a smoker. A Doppler ultrasound reveals that he has a 90% stenosis at the origin of the right internal carotid artery. This is a transient ischaemic attack (TIA).

Transient ischaemic attack (TIA)

This is a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without acute infarction. The previous definition with its arbitrary 24-hour time scale is no longer used as the end point is now tissue injury.

Examples include:

- anterior circulation – sudden transient loss of vision in one eye (amaurosis fugax), aphasia, hemiparesis; or
- posterior circulation – diplopia, ataxia, hemisensory loss, dysarthria, transient global amnesia.

TIAs may herald the onset of stroke (one-quarter of patients developing stroke have had a TIA, usually within the previous week).

The **ABCD² score** can help to stratify stroke risk in the first 2 days.

- | | |
|---|----------|
| • Age > 60 years | 1 point |
| • BP > 140 mmHg systolic and/or > 90 mmHg diastolic | 1 point |
| • Clinical features: | |
| Unilateral weakness | 2 points |
| Isolated speech disturbance | 1 point |
| Other | 0 points |
| • Duration of symptoms (min) | |
| > 60 | 2 points |
| 10–59 | 1 point |
| < 10 | 0 points |
| • Diabetes | |
| Present | 1 point |
| Absent | 0 points |

A score of < 4 is associated with a minimal risk, whereas > 6 is high risk for a stroke within 7 days of a TIA.

- If patients are at a high risk of a TIA, i.e. ABCD² score > 4, or have had two recent TIAs, especially within the same vascular territory, they should be admitted for investigation and treatment (see below).
- All patients should be referred to a TIA clinic and ideally seen within 24 hours. Investigation and treatment should be regarded as **urgent** and should be **completed** within 10 days.

Investigations

- Look for the source of the embolus – carotids (Doppler) and cardiac (echo).
- ECG.
- CT brain. Further investigation with MRI imaging of the brain and vascular system is often required.

Treatment

- Antiplatelet therapy as for stroke (p. 477).
- Modification of vascular risk factors – smoking, hypertension, statins as above.
- Early endarterectomy for symptomatic 70–99% carotid artery stenosis (within 1 week if possible).
- Anticoagulation for atrial fibrillation (p. 274) (aspirin 300 mg daily for 2 weeks, then anticoagulate with **heparin** and **warfarin** or **dabigatran**) (see p. 276).
 - **Progress.** In this patient an endarterectomy was performed. He has made lifestyle changes and has been well over the last 2 years.

Further reading

- Brott G, Hobson RW 2nd, Howard G et al. Stenting versus endarterectomy for treatment of carotid artery stenosis. *N Engl J Med* 2010; **363**: 11–23.
- Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. *Lancet* 2011; **377**: 1681–1692.

Case history (3)

A 40-year-old man presents with a 1-week history of headache followed by loss of speech and a right hemiparesis. His weakness worsens over the next 24 h and he becomes confused. A CT scan is normal at this time. A subsequent MRI scan reveals an infarct in the left frontal lobe with small haemorrhages elsewhere in the hemispheres. His ESR and autoantibodies are normal. CSF analysis reveals 35 lymphocytes/mm³ but is otherwise normal. A right frontal brain biopsy reveals **primary cerebral granulomatous angiitis** (a rare necrotising inflammation with granulomatous vasculitis of the brain and meningeal vessels). He is treated with high-dose steroids and cyclophosphamide.

What are the causes of strokes in this young age group?

In the younger age group, other causes of stroke, such as vasculitis or structural cardiac lesions, occur. In many of these conditions, specific treatment is indicated. Cerebral vasculitis is difficult to diagnose because systemic inflammatory markers may be normal. The CSF and intra-arterial angiography are sometimes also normal. Even a cerebral/meningeal biopsy may miss involved vessels because the condition is often patchy.

Investigations

Additional investigations in the younger age group:

- MRI head
- Autoantibodies, including anti-cardiolipin, ANCA
- Lupus anti-coagulant
- Serum electrophoresis

Investigations (continued)

- Serum lactate/pyruvate
- Urine for protein and casts
- Urine homocysteine
- Echocardiogram
- 24-h ECG
- Consider CSF analysis

- **Progress.** This patient was initially treated with high dose steroids and cyclophosphamide. The steroids were reduced gradually and oral cyclophosphamide continued for 6 months.

Further reading

Cramer SC. Brain Repair after Stroke. *N Engl J Med* 2010; **362**: 1827–1829.

SUBDURAL HAEMORRHAGE

This is caused by venous bleeding in the subdural space from rupture of a vein. It usually follows a head injury, often trivial.

Case history

A 77-year-old woman was admitted 2 weeks previously with failure to manage at home alone. There had been a 2-year history of cognitive decline that seemed to have accelerated to precipitate the admission.

On examination, she was confused, unable to repeat a five-digit number, disorientated and had an upgoing left plantar. Her Glasgow Coma Score (GCS, p. 492) was 12.

- **Diagnosis.** A CT scan revealed **bilateral subdural haematomas** (Fig. 15.7).

Subdural haemorrhage can present rather acutely following a fall with sudden onset of headache and diminished consciousness. The diagnostic challenge lies in identifying other cases that present vaguely without focal signs and with no history of trauma. A number of factors are associated with increased risk of apparently spontaneous subdural haemorrhage:

- old age
- cerebral atrophy, dementia
- alcohol excess, general debility
- bleeding diathesis/anticoagulant therapy
- intracranial lesion such as tumour
- brain surgery, especially ventricular shunt insertion for normal pressure hydrocephalus.

Management

The management of subdural haematomas depends on their size and the severity of symptoms. Small ones may simply be managed conservatively

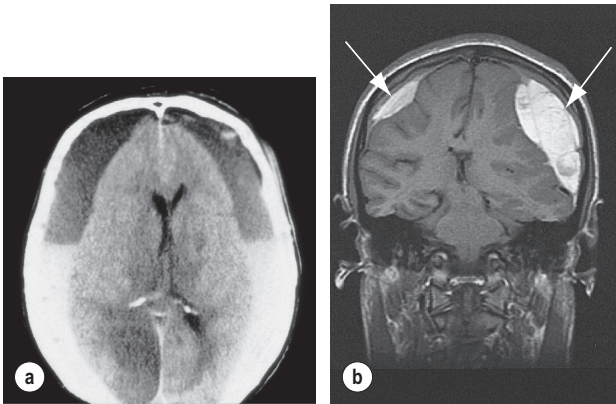


Figure 15.7 Bilateral subdural haematomas. a) CT scan b) MR (T1).

with follow-up CT scanning. Larger or more acutely symptomatic subdurals should be surgically evacuated.

- **Progress.** This patient had an acute subdural haemorrhage which precipitated her deterioration. This was managed surgically with overall treatment in her cognitive state.

PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disorder affecting nigrostriatal dopaminergic cells, as well as other brain cells.

It causes a combination of tremor, rigidity and akinesia, developing slowly over many months or years.

Case history

A 75-year-old man with Parkinson's disease presented with uncontrollable gyrating movements of his arms and legs. On obtaining a detailed history it transpired that he was on levodopa therapy. This had recently been increased to co-careldopa 50/200 (a mixture of carbidopa and levodopa) three tablets \times 4 daily.

What is the problem?

This patient has dyskinesia – a common, late side effect of levodopa (LD) therapy for parkinsonism. About 10% of patients per year of therapy will develop such dyskinesias, involving uncontrollable choreoathetoid movements and dystonic posturing. At this stage in the illness, the severity of dyskinesia is dose dependent and so a balance has to be struck between 'off' symptoms of bradykinesia and rigidity and 'on' dyskinetic symptoms. In this case, the co-careldopa was prescribed at too high a dose.

When commencing levodopa therapy, patients are generally started on co-careldopa 25/100 or co-beneldopa (100 mg/25 mg tablets: a mixture of benserazide hydrochloride and levodopa in proportions of 1 : 4) \times 3 daily. These drugs consist of a combination of levodopa and a peripheral DOPA decarboxylase inhibitor (DDI) to prevent inappropriate peripheral activation to dopamine. The dose of these drugs can be gradually increased in amount and frequency as the underlying disease worsens.

Alternatively, patients may receive a controlled-release preparation; co-careldopa 50/200 has nearly twice the bioavailable strength of straight careldopa but the co-beneldopa (25/1000) preparation is a more equivalent dose. The controlled release preparations may be given once at night to help with nocturnal or early morning 'off' symptoms, or may be given two to three times a day alone or in combination with straight levodopa in an effort to smoothen fluctuating symptoms.

Information

Some physicians start off with controlled release preparations. This is to minimise dose fluctuations that may result in dyskinesias later in the course of the disease, but there is no clear evidence for this protective effect.

Occasionally, dyskinesias occur in relation to dramatic fluctuations in levodopa levels rather than to high peak levels; the solution in this situation is to place the patient on a higher dose of longer-acting medication.

Other treatment available

- Exercise and physiotherapy are useful.
- Initiate pharmacological treatment when there is impairment/disability resulting from symptoms.
- Early treatment with monoamine oxidase B (MAOB) inhibitors (**selegiline** or **rasagiline**) may delay the need for more definitive dopamine replacement therapy by several months.
- **Dopamine agonists (DAs)** are used in patients below 70 years. Although they are less effective and less well tolerated than LD, they are also associated with fewer long-term motor complications.
- In older patients (i.e. more severely affected at diagnosis) start LD + DDI (**co-beneldopa** or **co-careldopa**) because of fewer side effects.
- Non-ergot DAs (**pramipexole** and **ropinirole** oral 3 times daily, or once daily with slow-release formulations, **rotigotine** via transdermal patch) are used in preference to ergot-derived drugs.
- All patients with PD will eventually require treatment with LD, often in combination with a DA. A typical starting dose is 50 mg of LD (e.g. **co-careldopa** 62.5 mg) 3 times daily, increasing after 1 week to 100 mg 3 times daily.
 - **Progress.** This patient was put on a lower dose of co-careldopa and the dyskinesia settled.

Further reading

Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet* 2009; **373**: 2055–2066.

MULTIPLE SCLEROSIS (MS)

MS is an autoimmune disease of unknown aetiology. It causes plaques of demyelination throughout the brain and spinal cord. Acute relapses are caused by focal inflammatory demyelination which causes a conduction block. These plaques can be demonstrated using an MRI scan (Fig. 15.8).

Case history (1)

A 28-year-old man presents with several days of pain and progressive loss of vision in one eye.

Examination showed diminished visual acuity 6/36 and disc swelling (papilloedema). He had previously had an episode of difficulty in walking and urinary incontinence which had recovered fully after several weeks.

What is the problem with his eyes?

The swelling of the disc, along with diminished visual acuity, suggests optic neuritis as other causes of papilloedema do not usually give visual disturbance. Optic neuritis is a common early presentation of multiple sclerosis (MS). The previous history suggesting an episode of transverse myelitis (inflammation of the cord) indicates dissociation in space and time, providing strong clinical support for the diagnosis of multiple sclerosis.

What action would you take?

- An MRI should be performed to look for demyelinating lesions of MS.
- CSF analysis for oligoclonal bands is usually unnecessary to further corroborate the diagnosis.
- Visual evoked potentials are likely to be delayed in the affected eye but may also reveal subclinical involvement of the other eye, providing evidence for dissociation in space.

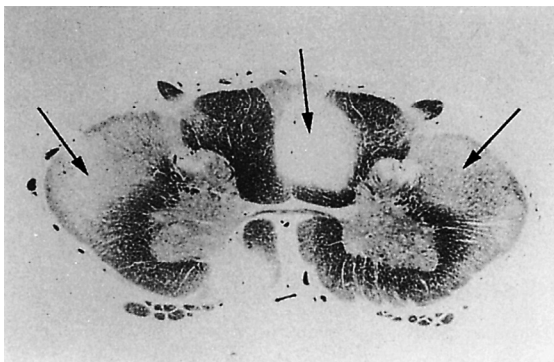


Figure 15.8 Multiple sclerosis – showing plaques in the posterior column and lateral corticospinal tracts. (Courtesy of the late Ian MacDonald).

- **Medication.** Recovery after an episode of optic neuritis is aided by intravenous methylprednisolone, e.g. 1 g/day for 3 days.
 - **Progress.** This patient's vision improved following his steroid therapy. However, the MRI showed demyelinating lesions of MS and he is being followed up in the Neurology Clinic.

Case history (2)

A previously well 25-year-old woman develops double vision, vertigo, unsteadiness, as well as speech and swallowing problems over 2 days. She is admitted to hospital where she rapidly deteriorates, becoming confused and hypoxic. She requires ventilatory support. An MRI scan reveals a number of small bilateral periventricular white matter lesions and lesions in the brainstem and cerebellar peduncles. She is given intravenous methylprednisolone and recovers well over the next 2 weeks apart from residual mild vertigo and intermittent diplopia.

Remember

Multiple sclerosis may sometimes present dramatically as a brainstem syndrome with central respiratory problems and rapid severe bulbar failure. Early supportive management and steroids is essential in such cases. There may be excellent recovery following the relapse. Patients with known MS who suffer a relapse involving bulbar function or dysarthria should similarly be carefully observed.

Case history (3)

A patient with known multiple sclerosis with frequent severe relapses, bladder instability and incontinence and painful leg spasms wonders if anything can be done for her incurable condition.

What would you suggest?

Many forms of treatment have been marketed, but none has been shown to improve outcome.

- **Acute relapses.** Short courses of steroids, such as IV methylprednisolone 1g/day for 3 days or high-dose oral steroids, are used widely in relapses and do sometimes reduce severity. They do not influence long-term outcome.
- **Preventing relapse and disability.** Beta-interferon (both INF β -1b and β -1a) by self-administered injection is used in relapsing and remitting disease. This is defined as at least two attacks of neurological dysfunction over the previous 2 or 3 years followed by a reasonable recovery. IFN β 1b is also used for secondary progressive MS. Interferon certainly reduces relapse rate in some patients and prevents an increase in lesions seen

on MRI. Unwanted effects are flu-like symptoms and irritation at injection sites. Beta-interferons are expensive.

- *Glatiramer acetate*, an immunomodulator, has been shown to reduce relapse frequency in ambulatory patients with relapsing remitting MS – similar to beta-interferon.
- *Natalizumab* is a monoclonal antibody which inhibits migration of leucocytes into the central nervous system by inhibitory α -4 integrins found on the surface of lymphocytes and monocytes. It is useful in severe, relapsing remitting MS that is unresponsive to other treatments. It is associated with a risk of progressive multifocal leucoencephalopathy (PML) and all patients need close surveillance for this and hypersensitivity reactions.
- *Alemtuzumab*, an anti-CD52 monoclonal antibody that destroys T- and B-cells, reduces disease activity.
- *Mitoxantrone* is used in primary progressive MS in specialist centres. It is potentially cardiotoxic and myelosuppressive.
- *New oral disease modifying drugs*, e.g. **fingolimod**, a sphingosine-1-phosphate receptor modulator, and **cladribine** (both given orally), an immunomodulator of lymphocytes, have shown benefit in ongoing trials.
 - **Progress.** This patient was admitted for reassessment. She was treated with baclofen for her spasms and spasticity and gabapentin for neuropathic pain. An anti-muscarinic (oxybutin) was tried for her urinary problems but eventually she was taught to self-catheterise herself intermittently. The physiotherapists, occupational therapists and a social worker were asked to review her. Disease modifying therapy was thought to be inappropriate for her advanced condition.

Further reading

- Chataway J, Miller DH. Multiple sclerosis – quenching the flames of inflammation. *Lancet* 2011; **378**: 1759–1760.
- Frohman EM, Wingerchuk DM. Transverse Myelitis. *N Engl J Med* 2010; **363**: 564–572.
- Pelletier D, Hafler DA. Fingolimod for multiple sclerosis. *New Engl J Med* 2012; **366**: 339–347.

ENCEPHALITIS

This is an inflammation of the brain parenchyma which is often due to a virus.

Case history (1)

A 45-year-old man presents with a one week history of malaise, followed by increasing confusion, headache, meningism and a seizure.

On examination he was confused, with a Glasgow Coma Score of 10. He had fever, neck stiffness and hyper-reflexia of the left arm and leg.

- **Diagnosis.** A tentative diagnosis of an **encephalitis** was made.

What action would you take?

- Supportive care: including respiratory support if necessary.
- Treatment of any seizures: ictal and post-ictal states are a reversible element of changes in conscious level.
- CT scan showed no space-occupying lesion.
- Lumbar puncture: there was a lymphocytosis.
- Serology and PCR: for likely aetiological agents (see below).
- **If there is even a remote possibility that the cause is HSV1, start aciclovir immediately, intravenous 10 mg/kg × 3 daily.** HSV is treatable; most other causes are not (Box 15.1). Patients have been known to relapse and respond to further treatment.

Remember

- Most cases of viral encephalitis present in the same way, the symptoms being milder than those for a bacterial meningitis. In many cases the viral cause can be worked out from the epidemiological pattern, e.g. from the geographical area where the disease was contracted and the season of the year.
- The term 'encephalitis' encompasses any acute febrile illness, perhaps with some meningeal involvement, that is accompanied by acute generalised or focal cerebral disturbance. Thus there is considerable overlap with meningitis.

Box 15.1 Causes of encephalitis/meningoencephalitis

- Viral include:
 - Herpes simplex (HSV 1 and 2)
 - Measles
 - Rubella
 - EBV
 - VZV
 - Echo
 - Coxsackie
 - CMV
 - HIV
 - Japanese B (most common worldwide)
 - Tick-borne encephalitis
 - Post-viral: acute disseminated encephalomyelitis (ADEM).
- Bacterial include:
 - Legionnaire's
 - Mycoplasma
 - *Listeria*
 - Tuberculosis.

In immunocompromised people think of unusual organisms, e.g. fungal.

Further investigations

- An MRI scan showed temporal oedema
- An EEG excluded generalised or complex partial status epilepticus
- If there is a possibility of immunosuppression (as a result of AIDS, lymphoproliferative disorders or iatrogenic) this should be investigated

- **Progress.** The MRI was highly suggestive of an *HSV1 encephalitis* and this was confirmed by serology and PCR. The patient was treated with IV aciclovir. Although he survived he was left with a significant residual deficit. He was sent for rehabilitation. He had problems with his memory, particularly common following HSV1 encephalitis.

Remember

- All cases of encephalitis in developed countries should be given aciclovir
- HSV is treatable; most other causes are not.

Case history (2)

A 25-year-old woman has an upper respiratory tract infection. Following recovery she becomes drowsy over a period of 48 h.

On examination she is apyrexial with a GCS of 9. She has abnormal eye movements and gaze-evoked nystagmus. There is marked spasticity in the limbs.

Investigations. CT shows effacement of cerebral sulci but it is safe to do a lumbar puncture. Lumbar puncture reveals 40 lymphocytes/mm³. She requires intubation to protect the airway.

A provisional diagnosis of HSV1 encephalitis is made.

Follow-on. A subsequent MRI scan reveals diffuse and confluent T2 hyperintensities in the periventricular white matter, in the brainstem and also within cerebral grey matter.

What is the diagnosis?

Acute disseminated encephalomyelitis (ADEM). This is considered to be a post-viral (sometimes post-mycoplasma), mainly white matter inflammatory condition, although the distinction from a direct viral encephalitis may be blurred. At the other end of the scale, the distinction from a severe initial attack of multiple sclerosis might also be unclear, although the latter attack is usually milder, more likely to be associated with CSF oligoclonal bands, and is characterised in retrospect with repeated attacks. However, treatment of both ADEM and multiple sclerosis attacks is similar, namely

with high doses of steroids. Because of the nature of presentation of ADEM, anti-virals are usually also given.

- **Progress.** She is treated with intravenous methylprednisolone followed by a course of oral steroids and made a good recovery after several weeks, with some residual pyramidal gait difficulty.

FALLS

Case history

A 70-year-old man presents with recurrent falls. On examination he has a rigid increase in tone, worse in the trunk than the limbs, marked bradykinesia and extreme mental slowness. He is unable to move his eyes vertical or laterally. He walks with a rather upright gait. He is thought to have Parkinson's disease but has had a poor response to levodopa.

What is the diagnosis?

This man has progressive supranuclear palsy (PSP; also known as Steele-Richardson syndrome). Parkinson's disease usually results in falls late on in the disease. Early falls should lead to suspicion of PSP or multisystem atrophy (which does not cause early cognitive problems).

Information

Steele-Richardson syndrome

- Parkinsonism
- Axial rigidity
- Dementia
- Defective upward-and-lateral gaze

Some common causes of falls are listed below. Some simply relate to stance or gait difficulties.

Causes of falls

Preserved consciousness:

- Leg weakness
- Spasticity
- Extrapyramidal syndromes
- Ataxia, periodic ataxia
- Vertigo
- Drop attacks
- Cataplexy
- Epilepsy, myoclonus

Loss of consciousness:

- Epilepsy
- Faint
- Syncope (cardiac or vascular insufficiency)
- Vertebrobasilar TIA
- Intermittent hydrocephalus
- Metabolic e.g. hypoglycaemia
- Toxic encephalopathy
- Other encephalopathies.

- **Progress.** This patient continued to deteriorate and died of pneumonia 6 months later.

Case history

A 65-year-old woman is worried she has epilepsy. She suffers repeated falls when walking outside. There is no warning before falling, she tends to graze her knees and hands and recovers immediately in a state of embarrassment. If she loses consciousness at all, it could only be for a split second because she is certainly aware when she hits the ground.

There is no abnormality on examination.

What is the diagnosis?

The diagnosis is *drop attacks*. These are benign episodes that commonly occur in middle-aged to elderly women. There is no loss of consciousness and they are not considered epileptic (see p. 503). They are due to sudden changes in lower limb tone, presumably brainstem in origin.

- **Progress.** This patient was reassured that she did not have epilepsy and was helped by using a walking stick.

Further reading

Dykes PC, Carroll DL, Hurley A et al. Fall prevention in acute care hospitals. *JAMA* 2010; **304**(17): 1912–1918.

TRAUMATIC BRAIN INJURY

Case history (1)

A 25-year-old man is knocked unconscious by a blow from a sledgehammer. He regains consciousness after a few minutes and attends A&E. He is nauseated and in pain but reasonably alert, with a Glasgow Coma Scale (GCS; Table 15.3) of 14. A skull X-ray shows a linear skull vault fracture. After being reasonably well for many hours his conscious level rapidly deteriorates to a GCS of 5. A subsequent CT scan reveals a large extradural blood collection that requires emergency drainage by craniotomy.

Extradural haemorrhage is a serious secondary effect of head injury. These bleeds occur into a tight space, resulting in a rather long lucid interval as the blood slowly accumulates. CT reveals a convex hyperdense collection in the acute phase. By contrast, subdural haemorrhages bleed more freely into a more easily opened space so the shape is concave on CT and there is little lucid interval.

Table 15.3 The Glasgow Coma Scale (GCS)

	Score
Eye opening (E)	
Spontaneous	4
To speech	3
To pain	2
No response	1
Motor response (M)	
Obeys	6
Localises	5
Withdraws	4
Flexion	3
Extension	2
No response	1
Verbal response (V)	
Orientated	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

Glasgow Coma Scale = E + M + V (GCS minimum = 3; maximum = 15)

- **Progress.** Following his craniotomy and drainage, he gradually recovered over the next few days. However, 2–3 weeks later he was still amnesic and needed constant attention. He is being followed up by the neurologists.

GENERAL MANAGEMENT OF TRAUMATIC INJURIES

Remember

- Always carefully monitor head injuries and record changes in GCS rather than simply considering one value in isolation
- The result of secondary swelling by haemorrhage or oedema (the latter is common in children) is raised intracranial pressure (ICP) leading to reduced perfusion pressure and coning.

Effects and complications of traumatic brain injury

- Primary effects:
 - Diffuse axonal injury
 - Contusion

- Laceration
- Vascular lesions.
- Secondary effects:
 - Extradural haemorrhage
 - Subdural haemorrhage
 - CSF leak, infection
 - Hydrocephalus
 - Compromised airway, respiration
 - Hypotension.
- Late sequelae:
 - Chronic daily headache
 - Post-traumatic stress disorder: rare
 - Vertigo
 - Cognitive impairment.

Information

Post-traumatic amnesia of over 24 h indicates severe brain injury.

What action would you take in a patient with a head injury?

- Attend first to any secondary or concomitant general problems, i.e. resuscitation, correct hypovolaemic shock, hypotension or compromised airway.
- Assess severity, using circumstances of injury and period of amnesia as a guide.
- Establish whether there is anterograde amnesia: the inability to form memories from the time of injury to the time of continuous normal memory, is the most accurate guide.
- Brainstem damage in head injury can affect central respiratory drive, bulbar function and pressor responses.
- Regular GCS measurements; below 5 at 24 h implies severe injury and 50% of such patients die.
- Do CT scan (see [Box 15.2](#)).

How would you manage the following problems?

- If the patient is deteriorating, or has evidence of raised ICP: consider insertion of a bolt, which is simply a tube into the ventricle through which ICP can be recorded.
- If ICP > 20 mmHg: need to treat; give enough mannitol IV to raise the plasma osmolality to 300 to decrease the intracranial pressure. However, the benefits of mannitol are still controversial. Mannitol also has poorly understood neuroprotective effects. Hyperventilation with IPPV will also lower the ICP.
- If the patient has haemorrhages: a craniotomy may be indicated.

Follow-up

Check for continued improvement in the weeks subsequent to the head injury. At 2–3 weeks post-injury, the development of hydrocephalus is a major complication.

Box 15.2 NICE Guidelines for head injuries**Criteria for immediate request for CT scan of the head (adults)**

- GCS less than 13 on initial assessment in the emergency department
- GCS less than 15 at 2 hours after injury on assessment in the emergency department
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (haemotympanium, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign)
- Post-traumatic seizure
- Focal neurological deficit
- More than one episode of vomiting
- Amnesia for events more than 30 minutes before impact.

Case history (2)

A 30-year-old man falls from a second-storey building and is immediately unconscious. He is admitted comatose, GCS 5, although he is breathing spontaneously. There are no external injuries and CT scan of the head is normal. He does not regain consciousness.

Diffuse axonal injury is the primary effect of traumatic brain injury and a common cause of vegetative state. There is usually immediate loss of consciousness followed by prolonged coma.

Milder axonal injury is reversible, e.g. in concussion. This damage occurs with brain accelerations or decelerations such as hitting the floor or wall, rather than by a direct blow to the head. The mechanism of damage is due to stretching of axons causing Ca^{2+} entry and neurofilament damage, interrupting axonal transport over the next 12 h. Certain areas are particularly vulnerable, such as the parasagittal white matter, internal capsule, cerebellar peduncles, posterior corpus callosum and dorsolateral midbrain.

- **Progress.** This patient was in a coma for a week and never recovered. Consent was obtained for his organs to be used for transplantation.

SEVERE BRAIN INJURY

Case history (1)

Your patient has had a severe hypoxic cerebral episode following a cardiac arrest. He is currently stable from a cardiac point of view but comatose (GCS 5) and requiring ventilatory support on ITU. He has been given 24 hours of induced hypothermia 32–34°. The ITU staff and the patient's relatives want an indication as to the likelihood of useful recovery.

What action would you take?

First, check for a remediable cause of coma or any confounding factors worsening the patient's responsiveness (see **Investigations** box). For example:

- Brain imaging may reveal a potentially treatable but unsuspected condition, possibly additional to the primary pathology, such as subdural or intracerebral haemorrhage or a hydrocephalus.
- An EEG may show abnormalities indicative of an unsuspected metabolic encephalopathy or subclinical seizure activity.
- The patient may still be under the influence of long-acting anaesthetic agents or other sedative drugs.

Investigations

- Brain imaging
- EEG
- Recent drug history
- Electrolyte imbalance
- Sepsis
- Ongoing low cardiac output

Aspects of examination to assess routinely

- Glasgow Coma Scale, *Table 15.3, p. 487.*
- Eye movements:
 - Following, roving, conjugate
 - Optokinetic nystagmus (following a moving grid pattern)
 - Vertical and horizontal doll's head movement
- Pupils
- Corneal reflexes
- Bulbar function: is he tolerating the ET tube?
- Respiratory function: level of ventilator support
- Tone and reflexes
- General examination, e.g. chest, infected pressure sores, abdominal guarding.

What are your prognostic indicators?

There are some prognostic values, depending on the time after the initial cerebral insult. The following criteria indicate **poor outcome**:

- Absent or extensor plantar response 72 hours after cerebral insult.
- Absent pupillary or corneal reflexes 72 hours after cerebral insult.

In general, every case must be assessed on its merits, especially with regard to the nature of the original insult and whether it was a discrete event or likely to be resulting in ongoing brain injury.

Note: relatives should not be given conflicting or inaccurate information.

Beware

Determination of brain death is made only by the appropriate consultant specialists who assess – on separate occasions – the various brainstem

reflexes and responses listed under 'Aspects of examination', above. The nature of the insult must be clear and remediable causes must be excluded. Because the criteria for brain death are heavily weighted towards brainstem function and, in the UK, EEG corroboration is not required, the locked-in syndrome (Table 15.4) should be excluded. In this state, a severe pontine lesion prevents access to or from the outside world. The only signs of relatively spared higher-level function may be preserved vertical optokinetic nystagmus or eye following, and preserved vertical doll's eye reflexes.

MENINGITIS

Case history (1)

A 55-year-old, a heavy alcohol user is brought to A&E with headache, confusion and a high fever.

On examination he is found to be photophobic and have neck stiffness. He is thought by the A&E staff to have meningitis and is immediately given IV benzylpenicillin because they were unclear about the most likely organism. You are called urgently to A&E.

Remember

Give immediate penicillin if meningococcal meningitis suspected.

What would you do?

You quickly check the neurological signs and agree this is meningitis. You also note that there is no purpuric rash of meningococcal septicaemia. You try and see his fundi but are unsure whether papilloedema is present. You are worried about doing a lumbar puncture because he is semi-conscious and you are concerned about the possibility of 'coning'. You arrange an immediate CT scan, which is normal. You proceed with a lumbar puncture and the CSF, which is turbid, is sent urgently to the microbiologists.

What do you do next?

Investigations

- Blood culture
- CXR

This man has meningitis, presumably bacterial. You recheck for purpuric spots of meningococcal meningitis.

Table 15.4 Differentiation diagnosis of the vegetative state

Condition	Vegetative	Minimally conscious	Locked-in syndrome	Coma	Brain death
Awareness	Absent	Present	Present	Absent	Absent
Sleep-wake cycle	Present	Present	Present	Absent	Absent
Response to noxious stimuli	±	Present	Present (in eyes only)	±	Absent
Glasgow Coma Scale score	E4, M1-4, V1-2	E4, M1-5, V1-4	E4, M1, V1	E1-2, M1-4, V1-2	E1, M1-3, V1
Motor function	No purposeful movement	Some consistent or inconsistent verbal or purposeful motor behaviour	Volitional vertical eye movements or eyeblink preserved	No purposeful movement	None or only reflex spinal movement
Respiratory function EEG activity	Typically preserved	Typically preserved	Typically preserved	Variable	Absent
	Typically slow wave activity	Insufficient data	Typically normal	Typically slow wave activity	Typically absent
Cerebral metabolism (PET)	Severely reduced	Insufficient data	Mildly reduced	Moderately to severely reduced	Severely reduced or absent
Prognosis	Varies: usually continued vegetative state or death	Varies	Depends on cause but full recovery unlikely	Recovery, vegetative state, or death within weeks	Already dead

NB: EEG and measures of cerebral metabolism are not required to make these clinical diagnoses. EEG, electroencephalography; PET, positron emission tomography; E, eye opening; M, motor response; V, verbal response.

From: The vegetative state: guidance on diagnosis and management. *Clinical Medicine* 2003; **3**: 251.

Information

Lumbar puncture

This should be performed with sterile measures. Check no papilloedema:

- Obtain patient consent
- Place patient in lateral decubitus position
- Identify L4–5 interspace (intersection of imaginary line between iliac crests and spine)
- Clean area with antiseptic, e.g. chlorhexidine
- Local anaesthetic (2% lidocaine) into skin and subcutaneous tissue
- Insert lumbar puncture spinal needle (bevel upwards) into skin over L4–5 interspace horizontally and slightly towards the head
- When needle penetrates the dura mater (slight decrease in resistance is felt), withdraw stylet and allow a few drops of CSF to escape
- Measure CSF pressure by connecting manometer to needle (normal CSF pressure is 60–150 mmH₂O); it rises and falls with respiration and heart beat
- Collect CSF in three sterile tubes (2 mL per tube)
- Send to laboratory. Note if clear, cloudy, yellow (xanthochromic) or red
- Remove needle and apply sterile dressing
- Patient should lie horizontal for 4 h to avoid headache.

Analgesics might be required.

Indications and contraindications are shown in [Table 15.5](#).

The CSF results sent through are:

- Protein: 1.5 g/L (normal range 0.2–0.4 g/L)
- Glucose: 1.5 mmol/L
- Leucocytes: 500/mm³
- Pneumococcus is seen on Gram stain.

Diagnosis

Pneumococcal meningitis. You immediately start treatment with IV cefotaxime 8 g daily in four divided doses because there is a high incidence of penicillin-resistant pneumococcus ([Table 15.6](#)).

Further reading

Thigpen MC, Whitney CG, Messonnier NE et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med* 2011; **364**: 2016–2025.

Causes of meningitis

- Bacterial:
 - *Meningococcus*
 - *Pneumococcus*
 - *Listeria* spp.
 - *Staphylococcus aureus*
 - *E. coli*
 - *Pseudomonas* spp.

Table 15.5 Indications and contraindications for lumbar puncture

Indications	Contraindications
Diagnosis of meningitis, encephalitis and subarachnoid haemorrhage (sometimes)	Raised intracranial pressure
Measurement of CSF pressure, e.g. for idiopathic, intracranial hypertension (IIH)	Local infections at site of puncture area
Removal of CSF therapeutically (IIH)	Platelet count $< 40 \times 10^9/L$
Diagnosis of conditions, e.g. neoplastic involvement	Mass lesion in brain or spinal cord

Table 15.6 Treatment regimens: antibiotics and acute bacterial meningitis

Organism	First choice	Alternative
Unknown	Cefotaxime	Benzylpenicillin and cefotaxime
<i>Meningococcus</i>	Benzylpenicillin	Cefotaxime
<i>Pneumococcus</i>	Cefotaxime	Penicillin if organism sensitive
<i>Haemophilus</i>	Cefotaxime	Chloramphenicol
<i>Listeria</i>	Amoxicillin + gentamicin	

This table shows the value of cefotaxime in clinical practice.

- Viral:
 - Enteroviruses
 - Mumps (meningoencephalitis).
- Atypical:
 - Tuberculosis
 - Cryptococcus
 - Leptospirosis.
- Non-infective:
 - Subarachnoid haemorrhage
 - Chemical meningitis.
- Recurrent:
 - Nasal sinus fistula
 - Traumatic CSF leak
 - Epstein-Barr virus
 - Sarcoidosis, Behçet's
 - Mollaret's meningitis (HSV type 2).
- **Pneumococcal meningitis** most commonly occurs in the debilitated or in those with a chest or sinus infection, valvular disease, splenectomy or a fistula from the paranasal air sinuses to the brain.
- **Meningococcal meningitis** (see also p. 7) occurs in epidemics and is sometimes associated with a petechial or purpuric rash and has a very

rapid evolution. It is seen in young adults. Nasopharyngeal swab culture is useful for typing meningococcus and haemophilus (see below).

- **Staphylococcus aureus meningitis** generally occurs in the context of systemic infection, abscesses or neurosurgical procedures.
- **Pseudomonas** and other Gram-negative enterobacillae are usually a consequence of surgical access to the CSF.
- **Listeria meningitis** is quite common. It should be treated with amoxicillin and gentamicin. It is also associated with an encephalitis.
- **Haemophilus influenzae** type B used to be extremely common but has been substantially reduced in many countries by immunisation (Hib vaccine) in children.
 - **Progress.** This man made an excellent recovery from his pneumococcal meningitis.

Case history (2)

A 22-year-old Asian man is admitted from A&E with an insidious 2-week history of malaise, headaches and marked confusion. On examination he is pyrexial, drowsy, has neck stiffness and has upgoing plantar responses. A presumptive diagnosis of **tuberculous meningitis** is made.

What action would you take?

- Routine blood tests.
- CXR: may show evidence of TB.
- CT scan: an immediate scan is done because with his confusion and possible raised intracranial pressure coning is a possibility following lumbar puncture. CT scan normal.
- Lumbar puncture.

The CSF results (Table 15.7) sent back to your house officer are:

Table 15.7 Typical changes in the CSF in meningitis

	Normal	Viral	Pyogenic	Tuberculosis
Appearance	Crystal clear	Clear/turbid	Turbid/purulent	Turbid/viscous
Mononuclear cells	< 5 mm ³	10–100 mm ³	< 50 mm ³	100–300 mm ³
Polymorph cells	Nil	Nil*	200–300/mm ³	0–200/mm ³
Protein	0.2–0.4 g/L	0.4–0.8 g/L	0.5–2.0 g/L	0.5–3.0 g/L
Glucose	2/3 to 1/2 blood glucose	> 1/2 blood glucose	< 1/2 blood glucose	< 1/3 blood glucose

*Some polymorph cells may be seen in the early stages of viral meningitis and encephalitis.

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- Glucose 1.8 mmol/L (blood level 6.5, i.e. low glucose)
- Protein 2.3 g/L (very high protein)
- 250 white cells (70% lymphocytes).

Note: the CSF protein can be so high as to cause the formation of a fine clot ('spider web').

Note: tubercle bacilli are only occasionally seen in the CSF and the CSF must be sent for culture, which takes 6 weeks.

How would you manage this case?

Start anti-TB chemotherapy on the basis of the clinical picture and high protein in the CSF, which strongly suggest tuberculous meningitis. Don't wait for the culture! Start therapy (rifampicin, isoniazid and pyrazinamide, for 6 weeks until the culture and sensitivities come back. Three drugs should be given for 3 months, followed by rifampicin and isoniazid for 9 months, depending on sensitivities. Specialist advice should be sought for treatment, notification and contact tracing.

- **Progress.** This patient made a good recovery. Prednisolone was also given for the first 3 weeks

Further reading

van de Beek D, de Gans J, Tunkel AR et al. Community-acquired bacterial meningitis in adults. *New England Journal of Medicine* 2006; **354**: 44–53s.

FITS AND FAINTS

Case history (1)

A 16-year-old young woman is referred with a suspected seizure. Earlier that day in her office she had felt unwell for about an hour. On getting up from her chair she suddenly lost consciousness without warning. She was incontinent of urine. She woke some minutes later, but had nausea and malaise for the rest of the day. Witnesses said that, when unconscious, she was flaccid, that her mouth, hands and feet were twitching and she was pale.

Is this a fit or a faint?

The patient has probably suffered a faint. Some factors are good at distinguishing a fit from faint (Table 15.8) whereas others are unreliable. In the above case, it is noted that faints, other than cardiac syncope, only occur on standing; the preceding symptoms are prolonged or ill defined. Twitching is not usually as violent as in a clonic seizure and the underlying muscle tone is not increased.

Investigations

- In suspected cardiac syncope include:
- ECG
 - 24-h ambulatory monitoring
 - Echocardiogram

Table 15.8 Features of fits and faints

	Fit	Faint
Prodrome	None or characteristic brief aura	Short or prolonged. Blood draining, visual darkening, rushing noise. Cardiac syncope may have no prodrome
Posture at onset	Any	Standing unless cardiac
Injury	Common	Rarer. Protective reflexes may act
Incontinence	Sometimes	Sometimes
Skin colour	Normal, flushed or pale	Pale
Recovery	Slow return of consciousness	Rapid, more physical weakness with clear sensorium
Frequency	Rare to many a day	Not repeated attacks each day
EEG	May be abnormal	Normal

Vasovagal faints are generally idiopathic but there are often precipitating or predisposing factors.

Associations with faints

- Adolescent, young adult female
- Low blood pressure
- Postural hypotension
- Heavy periods
- Micturition with prostatic problems
- Hot, stuffy surroundings
- Fasting, hypoglycaemia
- Dehydration
- Vagal stimuli such as distress or nausea.

Vasovagal attacks must be distinguished from cardiac syncope (see p. 265). In the latter there is often no warning, there may be breathlessness and engorged jugular veins and the heart rate may be faster than 140 or slower than 40.

- **Progress.** This girl and her parents were reassured that she had had a simple faint.

Case history (2)

A 16-year-old boy presents with repeated brief falls. He does not seem to lose consciousness but has been seen in A&E several times with severe head and facial injuries resulting from these episodes. Recovery, apart from associated injury, is immediate.

What is the diagnosis?

This history is suggestive of *atonic seizures*. This seizure disorder usually presents in childhood, often as one aspect of a complex epileptic syndrome. Not all seizures resulting in falls are generalised tonic-clonic in nature.

The loss of tone is immediate and absolute so that no protective reflexes occur and injury can be severe. Some sufferers need to wear crash helmets.

- **Progress.** He was referred to the neurologists for management of his epilepsy.

Epilepsy

An epileptic seizure is a convulsion or transient abnormal event experienced by the subject as a result of a paroxysmal discharge of cerebral neurones. Epilepsy, by definition, is the continuing tendency to have such seizures. Recurrent seizures can be prevented in most cases by anti-convulsant drugs.

Case history (3)

A 28-year-old man is brought to A&E because he was found to be unconscious and shaking in the high street. You are called to see him urgently because he has had a further tonic/clonic generalised seizure.

How would you manage this situation?

Remember

Status epilepticus exists when seizures follow each other without recovery of consciousness.

General measures

- Secure the airway; remove any false teeth and insert oropharyngeal tube.
- Administer 60% oxygen.
- Secure venous access: many anti-convulsants cause phlebitis, so choose a large vein.
- Glucose, 50 mL of 20% IV if hypoglycaemia is a possibility (see p. 221).
- Thiamine, 250 mg by slow IV injection if patient is a chronic alcohol user.

Control seizures

Remember

Full ventilatory support must be available when treating status epilepticus.

- Lorazepam 0.1 mg/kg by slow (2 mg/min) intravenous injection. Give rectal diazepam (10–20 mg) or intramuscular midazolam (0.2 mg/kg) if intravenous access difficult.
- If seizures continue give IV phenytoin:
 - Phenytoin: loading dose of 15 mg/kg at a rate not exceeding 50 mg/min. Give a further bolus up to total loading dose of 30 mg/kg if seizures persist. Continue with a maintenance dose of 100 mg IV at intervals of 6–8 h.

If seizures continue (despite phenytoin) use:

- Phenobarbital: 15 mg/kg at a rate not exceeding 100 mg/min and repeated at intervals of 6–8 h if necessary; IV clonazepam can also be used.
- If seizures continue despite these measures the patient is given a general anaesthetic, using thiopentone or propofol, and management is continued with full anaesthetic support.
 - **Progress.** This patient had no further fits after being given phenytoin. He was known to have epilepsy and was referred back urgently to his normal consultant for management of his drug therapy.

DIFFICULTY WALKING

Case history (1)

A 75-year-old man is referred with a 1-year history of progressive difficulty with his walking. He has hypertension which is well controlled with ramipril 5 mg daily. His wife says that his memory has been progressively getting worse.

On examination he has a mini mental score of 22, indicating a cognitive impairment. His grasp and snout (pursing of lips on lightly tapping the closed lips) reflexes are present, indicating frontal lobe disease. His legs are stiff and his walking is disorganised. This is an apraxic gait.

An apraxic gait is typical of frontal lobe pathology and can be regarded as a problem with high-level programming and execution of gait. This man has vascular dementia (multi-infarct dementia). Patients with cerebrovascular disease should always be imaged to exclude a frontal meningioma or other lesion.

- **Progress.** This patient was referred to the psychogeriatric department for full assessment. He was started on donepezil 5 mg daily (a reversal inhibitor of acetyl cholinesterase).

Case history (2)

A 70-year-old woman has a 3-week history of progressive difficulty in walking and loss of bladder function. For the last 6 months she has had problems with a stiff gait, numbness in the feet and pains down the left arm.

Continued

Case history (2) (continued)

On examination she has wasting and weakness of the hands and brisk triceps reflexes. In the legs there are signs of an upper motor neurone lesion with brisk reflexes and an extensor plantar response. There is also a patchy sensory loss in both arms and feet.

What is the diagnosis?

Cervical myelopathy, which at this age is most commonly due to spondylitis. She requires an urgent MRI scan of her cervical spine with a view to early decompression because relatively acute deficits are more potentially reversible. The MRI showed cord compression at the level of C5–6 (Fig. 15.9).

Walking difficulties with upper motor signs in the legs should always be investigated by cervical imaging. Thoracic compression is relatively much less common in the elderly age group.

Other common causes of difficulty in walking are:

- Neurological:
 - Myopathy: proximal, Trendelenburg positive (pelvis drops on the side of the stance leg suggesting weakness on abductor muscles of the hip), worse on stairs
 - Peripheral neuropathy: foot drop
 - Extrapyrarnidal, e.g. shuffling, stooped
 - Spasticity: stiff, circumducting hip
 - Apraxic: upright, high stepping
 - Ataxic: wide based.
- Rheumatological/orthopaedic conditions:
 - Polymyalgia
 - Hip joint disease.



Figure 15.9 MRI showing spinal cord compression. a) Multiple vertebral metastases (arrows); b) cervical compression caused by meningeoma (arrow).

- **Progress.** In view of this woman's serious disability and bladder problems, decompressive surgery was performed. This stabilised her condition but without improvement in her bladder function.

HEADACHES

Case history (1)

A 35-year-old woman is admitted to the Medical Admission Unit (MAU) with very severe headache of explosive onset. She is slightly drowsy with a Glasgow Coma Scale of 13 and she has photophobia and meningism.

A CT scan shows blood in the subarachnoid space (this has a 95% sensitivity in the first 24 hours).

- **Diagnosis. Subarachnoid haemorrhage.**
- Arrange for cerebral MR angiography to identify the source of bleeding.
- If aneurysm found, refer to neurosurgeon for surgical treatment.
- **Nimodipine** (e.g. 60 mg orally 4-hourly for 2–3 weeks, or 1 mg/hour IV) can reduce arterial spasm and reduce further cerebral infarction.
- Avoid hypotension (it may worsen the ischaemic deficit). Treat hypertension if diastolic pressure is persistently > 130 mmHg. Aim for a very gradual decrease in BP with careful monitoring and frequent repeat neurological examination.
- Supportive measures include bed rest, analgesia and laxatives (avoid sudden rises in ICP or BP).
- Watch for complications, including hyponatraemia (SIADH), hydrocephalus (obstruction of cerebral aqueduct by blood) and vasospasm causing ischaemic deficits.

NB. If the scan is negative and the history highly suggestive of a subarachnoid haemorrhage, a lumbar puncture is necessary.

- A **lumbar puncture** is performed to look for blood-stained CSF and xanthochromia (bilirubin discoloration of CSF due to cell lysis). Xanthochromia may be detected from ~12 hours to 3 weeks after SAH. Visible inspection of a centrifuged sample is often sufficient to detect xanthochromia, but laboratory spectrophotometry is more sensitive.

Remember

If a close family member has also had a subarachnoid haemorrhage then the rest of the family should be screened by MR angiography.

Conditions that can mimic subarachnoid haemorrhage include sudden onset of meningitis or viral meningitis, migraine, spontaneous subdural haemorrhage and post-coital headache. The last of these is a headache of

very sudden onset but is a benign self-limiting condition, perhaps a variant of migraine. With the availability of MR angiography, patients are now often scanned to exclude aneurysms. Finally, low-pressure headache may be of sudden onset. This is a poorly understood condition where headache may occur suddenly on standing and generally settles when lying down. There is meningeal enhancement on MRI and a low CSF pressure. The condition is again self-limiting. At least some cases relate to CSF leaks, sometimes from lumbar puncture (post-lumbar puncture headache), occasionally from Valsalva manoeuvres.

- **Progress.** In this patient, a posterior communicating aneurysm was found and she was treated with an intravascular coil insertion. She made a good recovery.

Further reading

van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007; **369**: 306–318.

Case history (2)

A 35-year-old man complains of continuous headache day and night. He used to have a different headache, which was episodic. This previous headache was unilateral, throbbing and would last a few hours; it was also associated with photophobia, visual scotomata and nausea. The new headache has no such features. He has to take about eight paracetamol tablets a day to control the pain.

What is this new headache due to?

Migraine headache, which was also the cause of this man's original headache. The headache sometimes becomes transformed into a more chronic headache punctuated by migraine-like exacerbations. Often the patient is given regular analgesia, which has a well-known effect of actually perpetuating headache.

What action should you take?

A brain scan is not often necessary in a clearly chronic headache with no signs, although the patient often expects one. It is more necessary to take a proper history and institute the correct management.

Management

Broadly similar for episodic migraine, i.e. sumatriptan prophylaxis is given if the sufferer has more than about two migraines a month or finds them very debilitating. A migraine prophylactic agent should be given (see p. 470).

- **Progress.** This patient was reassured that he did not have malignant or serious disease.

Chronic analgesia abuse should be stopped and he was advised to reduce this gradually over a month. He was told to expect that his headaches would be worse over this period.

Case history (3)

A 40-year-old man comes to A&E with severe headache, which then settles on arrival. This has happened before and he has always been discharged immediately. On taking a history, it transpires that he gets an excruciating headache that comes on gradually at about the same time every day. The headache is unilateral, pounding, involves the side of the face and is associated with a watering eye and nose. He jumps up and down in agitation with the pain. The symptoms generally only last about an hour.

What is the cause of this headache?

This description is typical for **cluster headache**. Each cluster may last a few weeks, with several months of relief in between.

Cluster headache

Cluster headache is distinct from migraine and consists of recurrent bouts of excruciating unilateral pain that typically wake the patient. Attacks cluster around one eye. Cluster headache affects adults, mainly males aged 30–40 years. Alcohol and glyceryl trinitrate can provoke attacks. Severe pain can last for several hours and is associated with vomiting. One cheek and nostril become congested. Transient ipsilateral Horner's syndrome is common. One bout of cluster attacks, with pain every few nights, usually lasts 1 to 2 months. Despite excruciating pain there are no sequelae. Bouts recur at intervals over several years but tend to disappear after the age of 55.

- **Progress.** In this patient, treatment with analgesics and prophylactic migraine drugs did not help. However, his attacks were attenuated with subcutaneous sumatriptan. Oxygen inhalation also helped on occasions. A short course of oral prednisolone reduced the frequency of attacks.

Case history (4)

A 30-year-old woman has a long history of short but severe headaches on one side of the face, lasting only a few minutes but occurring several times a day. There is considerable flushing and rhinorrhoea on the same side during each attack. There is no trigger to the attacks.

What is the cause of this headache?

The patient has **paroxysmal hemicrania**; the attacks are longer in duration than in trigeminal neuralgia but shorter than in cluster headaches or migraine. There is generally some associated autonomic disturbance, as seen here. There is a specific and often extremely rewarding response to indometacin, as occurred in this woman.

Some causes of acute, episodic and chronic headache are given in [Box 15.3](#).

Box 15.3 Causes of headache

- Very sudden headaches:
 - Subarachnoid haemorrhage
 - First migraine attack
 - Subdural haemorrhage
 - Meningitis, encephalitis
 - Inflammatory meningoencephalitis, e.g. SLE
 - Cerebral abscess
 - Raised intracranial pressure
 - Low-pressure headache
- Episodic:
 - Tension headache
 - Migraine
 - Paroxysmal hemicrania
 - Cluster headache
 - Trigeminal/occipital neuralgia
 - Giant cell arteritis (temporal or cranial arteritis)
 - Post-coital headache
- Chronic:
 - Tension headache
 - Analgesia abuse
 - Chronic hemicrania
 - Chronic cluster headache
 - Cervicogenic headache
 - Space-occupying lesions
 - Raised intracranial pressure
 - Ongoing after many acute headaches
 - Associated with depression/anxiety

MOVEMENT DISORDERS

- Akinetic-rigid syndromes, i.e. slowed movement with increased tone.
- Dyskinesias – added, uncontrollable movements.

Both may co-exist.

Case history (1)

A 22-year-old woman develops an acute gastrointestinal illness with abdominal pain, vomiting and diarrhoea. After 2 days she becomes generally stiff and has prolonged episodes of painful spasm of the axial muscles with opisthotonic posturing. Her eyes periodically roll upwards involuntarily (oculogyric crises). She had been given metoclopramide for her vomiting.

- **Diagnosis.** Oculogyric crises from metoclopramide.

Acute dystonic reactions can occur in sensitive individuals after relatively modest doses of drugs with central anti-dopaminergic action, such as

neuroleptics or certain anti-emetics, e.g. metoclopramide. Neuroleptic malignant syndrome can also occur.

Treatment of oculogyric crisis involves the identification and stoppage of the responsible agent. These acute dystonias respond generally to intravenous centrally acting anti-muscarinics, e.g. procyclidine 5–10 mg.

Anti-emetics, e.g. domperidone, ondansetron or granisetron do not produce dystonia.

Hypokinetic movement disorders

- Parkinson's disease
- Multisystem atrophy
- Progressive supranuclear palsy
- Dementia with Lewy bodies
- Corticobasal degeneration
- Some frontal dementias, mass lesions
- Tardive dyskinesia (+ hyperkinetic)
- Psychomotor retardation.

Hyperkinetic movement disorder

- Choreoathetosis
- Ballismus
- Dystonia
- Myoclonus
- Tics
- Tremor
- Psychogenic.
 - **Progress.** This woman was given IV procyclidine 5 mg IV. Her dystonia settled within 24 hours.

Case history (2)

A 40-year-old man has a 1-year history of involuntary facial movements and a shuffling gait. There is a past history of schizophrenia, for which he was given haloperidol. On examination he has intermittent involuntary protrusion of his tongue, grimacing and blepharospasm. He has some writhing movements of his left arm and repetitive rubbing of the soles of his feet on the floor when sitting. Voluntary arm movements are slow. He walks slowly with a shuffling gait and stooped posture.

- **Diagnosis. Tardive dyskinesia.** This develops in patients previously, as well as currently, on anti-psychotic medication. The movement disorder may be a complex mixture of hyperkinetic restlessness (akathisia), dystonia and choreoathetosis, and hypokinetic bradykinesia. They are late and difficult to reverse. The effects of anti-dopaminergics are thought to be due to long-term dysregulation of dopaminergic pathways. Sometimes, in the short term, increases in anti-psychotic drug doses actually temporarily improve the hyperkinetic aspects (direct anti-dopaminergic action), but this is likely to lead to worsened long-term problems. The drugs that are good for

avoiding acute extrapyramidal side effects are also good for minimising long-term side effects.

- **Progress.** In this patient the haloperidol was gradually reduced and stopped. His symptoms improved. He has been told of the risk of recurrence on further anti-psychotic therapy.

GUILLAIN-BARRÉ SYNDROME

This is an acute sensori-motor polyneuropathy which often follows a gastrointestinal, e.g. *Campylobacter*, cytomegalovirus, or a respiratory infection.

Case history

A 34-year-old woman is brought to A&E by her relatives; she has a 1-week history of difficulty walking. She had had mild gastroenteritis due to *Campylobacter jejuni* about 5 weeks before but had recovered from this. Her relatives thought she was 'putting it on' but became a bit concerned when they found that she was unable to climb the stairs to her flat.

On examination she looked well and was orientated; but she was extremely anxious because she thought she was becoming paralysed. She had a symmetrical weakness in her limbs, which was worse proximally. Reflexes were absent and she had normal plantar responses. There was a mild sensory deficit of a glove and stocking distribution

What is the diagnosis?

This could be the Guillain-Barré syndrome. Do *not* leave this patient unattended because the progression can be fast and her respiratory muscles can be affected within a few hours.

Investigations

Blood tests:

- FBC
- U&Es
- CRP
- ABGs

What should you do?

Admit her. Once on the ward, perform a lumbar puncture. In this patient, the CSF protein is raised. She gets progressively weaker and is having difficulty breathing,

How would you manage this patient?

- Admit her to the HDU.
- Regularly monitor her respiratory function with vital capacity. Intubation and ventilation might be required. Call for expert help.

- Nursing care: to avoid pressure ulcers.
- Prophylaxis: to prevent venous thrombosis (LMW heparin, enoxaparin).
- Steroid therapy is ineffective.
- IV immunoglobulin given in the first 2 weeks reduces duration and severity of weakness. NB. Check IgA levels; severe allergic reactions occur (due to IgG antibodies) with IgA deficiency.
 - **Progress.** This patient was given IV immunoglobulins and gradually improved over the next few months.

Prognosis

80% of patients make a full recovery, as occurred in this patient.

SPINAL CORD COMPRESSION

This produces radicular pain at the level of the cord lesion, with a spastic tetraparesis or paraparesis below the level; sensory loss below the cord level is also present.

Case history

A 56-year-old man is admitted with a 2-week history of weakness in his legs. He has no other complaints but admits that he is a heavy smoker.

On examination there is weakness of both legs, which is more marked distally; the left leg is more severely affected. Knee and ankle jerks are slightly brisk and he has a bilateral extensor plantar response. There are no sensory signs. He has no neurological deficit in his arms.

NB. This is a medical emergency.

This patient has a mild paraparesis and a cord lesion must be excluded.

Investigations

- Routine bloods show a Hb of 100 g/L with an ESR of 100 mm/h.
- CXR was normal, making carcinoma with secondaries unlikely despite him being a heavy smoker.
- Thoracic and lumbar spinal X-rays showed an osteolytic lesion at T10. The preliminary tests have taken 3 days and the patient is now incontinent of urine and his leg weakness is worse. Urgent neurological referral is required.

MRI scan shows a lesion at T10. Urgent decompression is performed by a neurosurgeon but the patient still requires a urinary catheter.

Further blood tests

- Serum protein electrophoresis and immunofixation shows a monoclonal band.
- Bence Jones protein is present in the urine.
- Bone marrow shows infiltration with plasma cells.
 - **Diagnosis.** Multiple myeloma.
 - **Progress.** This patient needed radiotherapy and chemotherapy. He still requires a catheter and is mobilising only slowly with a frame.

Remember

Diagnosis is urgent with cord compression. Prompt diagnosis enables decompression to be performed before severe symptoms develop and potentially before urinary problems, which if present are frequently permanent, even with decompression.

DELIRIUM (see also p. 153)

Delirium is the most commonly misdiagnosed psychiatric disorder in the general hospital and many cases go undetected. Yet it is the most common psychosis met in the hospital setting; 10–20% of surgical and medical inpatients have delirium during their admission. It is the best indication that the higher centres of the brain are failing.

Information

Delirium: central features

- Impaired consciousness/attention
- Global disturbance of cognition
- Psychomotor disturbance
- Disturbed sleep/wake cycle
- Emotional disturbance

Case history

You are asked to see a 68-year-old man who had surgery for a fractured hip sustained after a fall at home 3 days previously. He was awake all night, occasionally shouting out, disturbing the rest of the ward, and he keeps pulling at his intravenous line.

How would you diagnose delirium?

An acute onset and fluctuating course is valuable diagnostically. Delirium represents an acute generalised impairment of cognitive function (see [Information](#) box). The primary feature is disorientation in time and place (more rarely person). A well patient should know the day of the week, month and year (people who are well can occasionally get the date and time wrong). They should know that they are in hospital, its name and location, and the name of the ward. Other psychoses do not affect orientation.

- **'Clouding of consciousness'**: refers to the variable level of attention seen in delirium, so that the patient cannot learn information and therefore cannot recall it.
- **Visual hallucinations or illusions**: are commonly present, so the patient may mistake a curtain movement in a dimly lit ward as a threatening person, resulting in extreme fear and agitation, especially at night.

- **Persecutory delusions:** are the most common and may make patients refuse food, drink and medicines because they believe that they are being poisoned. Alternatively, these delusions can cause aggression as patients defend themselves against a perceived threat.

Remember

- Behaviour may be agitated and disturbed or 'quiet', 'hypoactive' and less easily identified
- Fluctuating presentation and disturbed sleep/wake cycle may conceal abnormalities during the day
- Emotional disturbance (fear, perplexity, apathy, depression) is common in delirium.

What were the predisposing factors in this patient?

Delirium occurs most commonly in a person with a developing or deteriorating brain, with risk factors such as:

- Extremes of age (the young and old)
- Brain damage or insult:
 - Any dementia (most common)
 - Previous head injury or episode of delirium
 - Previous cerebrovascular accident
 - Alcoholic brain damage
- Newly prescribed or multiple medications
- Prolonged operative procedure and anaesthesia
- Immobilisation and social isolation
- Dislocation to an unfamiliar environment (such as admission to hospital)
- Sleep deprivation
- Sensory deficits (e.g. visual or hearing) and extremes (overload or deprivation).

Specific causes of delirium include:

- Brain trauma
- Epilepsy (ictal, interictal, postictal)
- Neoplasm (intracranial or extracranial)
- Other brain-space-occupying lesions (e.g. abscess)
- Metabolic encephalopathies (e.g. hypoglycaemia, hypoxia, hyponatraemia)
- Infections (intracranial and systemic)
- Drugs and poisons (see p. 519)
- Withdrawal from drugs (e.g. alcohol and sedatives; see p. 521)
- Vascular (cerebral or myocardial)
- Haematological (severe anaemia)
- Extracranial insult (e.g. hypothermia).

How would you investigate this patient?

Corroborative history from family/partner (duration of history, drug history, past medical and psychiatric history, alcohol/drug use).

An EEG shows excess slow waves in 90% (with the exception of drug withdrawal states) and may show sharp waves and spikes in status epilepticus. It is used occasionally as a confirmatory test, if there is doubt about the clinical diagnosis.

Investigations

- Look for infections (MSU, CXR, blood and sputum cultures, lumbar puncture if indicated)
- U&Es (hyponatraemia)
- Calcium
- Blood sugar
- Liver and cardiac enzymes
- ECG (silent myocardial infarct)
- CT brain scan ('silent' parietal infarct; predisposing brain disease/damage)

Second-line investigations:

- Therapeutic drug levels (anti-convulsant, lithium)
- Endocrine (TFTs)
- Vitamin deficiency (thiamin, nicotinic acid, B₁₂)
- Illicit drug screen

Nursing care

A carefully controlled consistent and balanced environment is essential:

- Single room, if available
- Windows that do not allow exits
- Minimal stimulation by noise
- Persistent orientation by nurses and notices (a very disturbed patient may require one-to-one nursing temporarily)
- Minimal visitors: only those the patient knows well
- Some lighting at night
- Reverse dehydration and do not neglect nutrition
- Treat constipation, sleep disturbance
- Perceptive aids, e.g. glasses, hearing aid.

Management

- Delirium requires urgent management because complications (e.g. falls, pressure ulcers and infections) can exacerbate the condition and contribute to significant mortality, particularly in the elderly.
- Find the cause and reverse it.
- A psychiatric opinion can be useful regarding differential diagnosis (see below) and management.
- Reduce all drug treatments to a minimum (see p. 521). Avoid anti-psychotic drugs unless the patient is a danger to him- or herself (or others), is distressed or if the patient's general health is suffering.
- Symptomatic treatments include anti-psychotic drugs, initially in small doses, avoiding strong anti-muscarinics.
- Evaluate progress regularly.

Differential diagnosis

- Other organic brain disorders:
 - Lewy body dementia: fluctuating conscious level and extreme sensitivity to psychotropic drugs
 - Advancing dementia, acute on chronic disturbance.
- Functional psychoses/mood disorders:
 - Severe depression (agitation, psychomotor retardation, persecutory ideas)
 - Mania/hypomania (fluctuating mood, nocturnal disturbance, abnormally heightened perceptions).
- Drugs: delirium tremens (see p. 525).

Drug therapy

Doses of tranquillising drugs should start low and be titrated depending on age (this patient is 68 years old), pre-existing brain damage and response to initial treatment. Patients with delirium are often sensitive to medication and the dose needs to be balanced carefully.

- Haloperidol by mouth: 1.5 mg then 1.5–5 mg up to three times a day depending on level of disturbance, sensitivity to drug and response. *Note:* liquid or tablet form; lowest effective dose; beware extrapyramidal side effects.
- Phenothiazines are best avoided because of their anti-muscarinic and alpha-blocking actions.

If intramuscular medication is required

- Haloperidol 0.5 to 1.5 mg IM, together with lorazepam 0.5–1 mg.
- Repeat 8-hourly as necessary.

These drugs should not be given intravenously. If the patient is sensitive to medication and extrapyramidal side effects (EPSEs) are likely or present, use an 'atypical' anti-psychotic drug, such as risperidone (starting at 0.5 to 1 mg orally). Check doses carefully. Reversal of acute EPSEs can be achieved with a low dose of an anti-muscarinic drug (e.g. procyclidine 5 mg oral/IM).

- *Progress.* Delirium resolved in this patient after 48 h following oral haloperidol. This anti-psychotic medication was tailed off gradually over 1 week.

Remember

Extrapyramidal side effects of anti-psychotic medication:

- Acute dystonic reactions: involuntary muscle contractions involving extra-ocular muscles, face, neck, mouth and tongue
- Pseudoparkinsonism: rigidity and tremor in larger muscles.

What is the prognosis?

There is often a delay of a few days when the underlying condition has improved but the brain is still dysfunctioning. Otherwise the prognosis depends on the successful treatment of the main aetiological condition (up to 20% undetermined in the elderly) and the state of the pre-existing brain (25% of the elderly with delirium will have an underlying dementia). Good

communication with the patient's primary care doctor is essential because treated as well as unrecognised delirium can cause problems after discharge.

Further reading

Inoye SK. Delirium in older persons. *New England Journal of Medicine* 2006; **354**: 1157-1165.

DRUGS AND POISONS AS CAUSES OF DELIRIUM

Delirium can occur in response to excessive or normal doses of many drugs, particularly in the elderly. Some drugs are more likely to cause delirium than others.

Case history

An 83-year-old woman is discharged from hospital following an admission for severe breathlessness due to acute on chronic heart failure. She was discharged on furosemide, lisinopril, carvediol and spironolactone.

Three weeks later she is brought to A&E by her carer because she is confused, very aggressive towards her carer and unaware of where she is.

On examination she is conscious but completely disorientated in time and place. She is unaware that she is in hospital. Cardiovascular examination shows a pulse of 60 per minute, irregularly irregular, normal venous pressure and no basal crackles or ankle oedema.

You check on her medication with the carer who confirms that she takes the drugs given to her when she left the hospital on a regular basis. The carer also says she now takes an additional drug which has been given to her by her doctor because of an irregular pulse.

Unfortunately, the carer has not brought all the drugs with her. You contact the patient's doctor who says that she prescribed digoxin because of the irregular pulse, which she thought was atrial fibrillation.

You think this might be the problem, so you check her digoxin levels as well as her urea and electrolytes.

DRUGS CAUSING DELIRIUM

Cardiac drugs

- Digoxin: check serum level
- Calcium channel blockers
- Anti-arrhythmics, e.g. lidocaine
- Beta blockers: especially propranolol (lipid soluble); use water-soluble beta blocker, e.g. atenolol.

Therapeutic drugs affecting the brain

- Benzodiazepines: although withdrawal is a more common cause; see below
- Barbiturates: withdrawal again more commonly
- Other hypnotics: nitrazepam
- Lithium: usually a sign of toxicity
- High-potency anti-psychotics: neuroleptic malignant syndrome (see [Information](#) box, below)
- Anti-convulsants: usually a sign of toxicity
- Dopamine and its agonists: levodopa and bromocriptine.

Drugs with anti-muscarinic properties (common cause of delirium)

- Atropine and scopolamine: remember eye drops and pre-meds in anaesthesia
- Other topical cycloplegics and mydriatics
- Anti-parkinsonian agents: in patients with both Parkinson's disease and pseudoparkinson's, caused by dopamine antagonists
- Anti-depressants: especially tricyclics; amitriptyline most frequently
- Anti-psychotics: commonly the phenothiazines, especially chlorpromazine
- Anti-emetics
- Anti-histamines
- Anti-spasmodics: uncommon.

What are the physical signs of the anti-muscarinic state?

- Dilated and poorly reactive pupils (blurred vision)
- Flushed face
- Dry mouth and skin
- Fever
- Tachypnoea
- Tachycardia
- Hypertension
- Urinary retention and diminished bowel sounds.

How would you treat anti-muscarinic-induced delirium?

- General supportive nursing measures (see [p. 517](#))
- Management usually conservative with observation of vital signs
- IV line and ECG Monitor if symptoms marked
- Oral or IM benzodiazepine (e.g. diazepam 10 mg adult dose) for agitation or seizures
- Cholinergic therapy with an anticholinesterase (physostigmine) is potentially hazardous (heart block, bronchospasm, respiratory failure) and used, if at all, for life threatening cases (uncontrolled seizures, coma, respiratory depression). Discuss with senior and/or poisons unit.
 - **Contraindications:** ischaemic heart disease, prolonged PR, QRS intervals, asthma, diabetes, inflammatory bowel disease, bowel or bladder obstruction, glaucoma, pregnancy, hypothyroidism.

Anti-infective agents

- Anti-malarials, e.g. chloroquine and mefloquine
- Antibiotics: uncommon, but associated diarrhoea may lead to dehydration.

Gastrointestinal drugs

- H₂ antagonists: cimetidine most commonly reported
- Bismuth chelate.

Anti-inflammatory

- Non-steroidal anti-inflammatories (NSAIDs)
- Corticosteroids: differential diagnosis of affective and paranoid psychoses
- Interferons.

Chemotherapeutic agents

- Crisantaspase (asparaginase)
- Methotrexate
- Vinca alkaloids.

Anaesthetic agents

- Ketamine.

'Recreational' drugs

- Alcohol (toxic levels)
- Amphetamine
- Ecstasy (methylenedioxymethamphetamine, MDMA): an amphetamine-like drug
- Lysergic acid (LSD) and other hallucinogens (magic mushrooms)
- Cannabis (toxic doses)
- Cocaine
- Phencyclidine ('angel dust'): chemically related to ketamine
- Gamma-butyric acid.

Poisons

Exposure can be occupational, environmental or by deliberate self-ingestion, e.g.:

- Methanol
- Solvents: adolescents
- Carbon monoxide
- Plant alkaloids
- Many industrial chemicals: always find out the patient's occupation.

How do you treat drug-/poison-induced delirium?

- Stop the delivery of the drug or poison. If in doubt, stop all non-essential medication, and/or reduce the dose.
- Treat specific causes (e.g. hyperbaric or mask-delivered oxygen for CO poisoning).
- General measures are covered in the section on delirium (see p. 517).

Drug withdrawal

- Alcohol (see p. 527).
- Sedatives:
 - Benzodiazepines
 - Barbiturates.

Clinical presentation of sedative withdrawal (beyond delirium)

- Mental: anxiety, irritability, agitation, insomnia, nightmares.
- Arousal: tremor, sweating, tachycardia, sensitivity to light, noise and touch, muscle tension, uncommonly convulsions (with the exception of barbiturate withdrawal).
- Physical: nausea, anorexia, 'flu-like' symptoms, metallic taste.

Treatment of sedative withdrawal

- Replace the original class of drug in adequate doses to control the withdrawal symptoms, reducing to the minimum amount to prevent their re-emergence.
- Try to use a long-acting drug (e.g. diazepam), although sometimes the original drug itself is required.
- Therapeutic drug cessation can be achieved gradually later but the patient should be monitored closely and supported. Even patients with long-term dependence can manage some reduction and stabilisation on a reduced dose in the short term.

Remember

Check doses with a senior colleague and with the national formulary.

- **Progress.** This woman's digoxin level was 2 µg/L (toxic range > 1.5 µg) so that her digoxin was stopped but her other medication continued. Her serum urea and electrolytes were normal, the serum potassium was 4.3 mmol/L.

Her delirium required a small dose of oral haloperidol 0.5 mg × 2 daily for the first 4 days. She progressively improved and was discharged after 9 days, back to her normal self. In view of her age she was started on aspirin 150 g daily (not warfarin) and digoxin 62.5 µg daily for her atrial fibrillation.

DEMENTIA

See also p. 156.

Dementia is the most common organic brain syndrome seen in elderly inpatients; 7% of people over the age of 65 and up to 33% over the age of 85 have a dementing illness. Treatable causes can be found in 10% of patients with definite dementia, but that figure is considerably higher if the 'pseudodementia' of depressive illness is included.

Dementia is a global, acquired, progressive deterioration of intellect, memory and personality. Altered ('clouded') consciousness is not usually involved, in contrast to delirium, although dementia is often an underlying predisposition for delirium (see p. 515).

Case history

A 74-year-old woman is brought into A&E having been found wandering in the street at night. She is poorly nourished, dishevelled and has several bruises on her arms and legs. You find out from her daughter that her husband died 6 months previously.

How does dementia present?

- Loss of memory, especially short term
- Episodes of increasing 'confusion'
- Falls, with or without head injury
- Wandering and getting lost (getting into the wrong bed), especially at night
- Insomnia
- Weight loss
- Slow recovery and mobilisation after injury (e.g. hip fracture) or illness (e.g. myocardial infarct, pneumonia)
- Incontinence
- Difficulty dressing: parietal lesion of dressing dyspraxia
- Behavioural disinhibition: frontal lobe sign
- Severe extra-pyramidal reaction to dopamine antagonists: Lewy body dementia.

What are the causes?

Information

Causes of dementia (see Table 7.2 for treatable causes)

Common causes:

- Over 65:
 - Alzheimer's disease
 - Multi-infarct dementia
 - Lewy body disease
 - Parkinson's disease
- Under 65:
 - Alzheimer's disease
 - AIDS
 - Alcoholic dementia
 - Head injuries

Less common causes:

- Prion disease (Creutzfeldt-Jakob)
- Huntington's
- Fronto-temporal dementia (Pick's)
- Multiple sclerosis
- Wilson's disease

Differential diagnosis

- Delirium
- Amnesic syndrome: relatively specific memory loss, e.g. Wernicke-Korsakoff syndrome (see p. 527).
- Depressive 'pseudodementia'
- Learning disability ('amentia').

Investigations

- A corroborative history: duration, presentation, mood, alcohol, past history
- A Mini Mental State Examination (MMSE): a brief, structured bed-side screening test of memory
- Intelligence quotient (IQ) (performed by a psychologist) to confirm cognitive decline
- Blood tests:
 - Gamma glutamyl transpeptidase and mean corpuscular volume: raised levels are evidence of excess alcohol
 - Urea, creatinine, eGFR
 - Liver enzymes
 - Free T4 and TSH
 - VDRL
 - Haemoglobin
 - ESR or CRP
 - Autoimmune screen to include ANA
 - Serum electrophoresis
 - Glucose levels
 - Vitamin B₁₂ and red cell folate
 - Calcium
- HIV testing after counselling in at-risk group
- MSU
- CXR
- CT/MRI brain scan: tumour, subdural haematoma, normal pressure hydrocephalus and infarcts *might* confirm generalised cerebral atrophy
- ECG: arrhythmias
- EEG: diffuse slow waves are rare before 75 in normal health. A normal EEG would suggest an alternative diagnosis
- Consider lumbar puncture, if diagnosis is unclear

Examination

- Cardiovascular, neurological and endocrine system: to exclude secondary causes.
- Mental state examination.
- Simple cognitive screening bedside tests: dementia may be suggested by the quality of the responses, e.g. 'perseveration' (repeating a response beyond the relevant question), 'confabulation' (inventing recollections to compensate for memory loss).
- Look for depressed affect.

Information

Simple cognitive screening

- Orientation in time, place and person: ask day, month, year; ward, hospital, town/city, country; identity of relatives or key ward staff
- Attention and concentration: ask patient to recite the days of the week, or the months of the year, backwards (should be 100% accurate)
- Verbal short-term memory: teach patient to immediately recite a name and address accurately (a test of registration: they should be able to do this in two attempts). Then ask the patient to recall the name and address 5 min later (test of memory recall; should recall 95% of the individual items)
- Long-term memory: tests of general information, e.g. recent news, world events or on a subject of their interest
- Premorbid intelligence (necessary to judge whether there has been a deterioration in intellect): establish level of education achieved and occupation

How would you manage a case of dementia?

- Treat any reversible cause.
- Stop anti-muscarinic drugs, if possible.
- Involve a psychiatrist early regarding diagnosis and management.
- Acetyl cholinesterase inhibitors may be indicated in early Alzheimer's disease (e.g. donepezil, galantamine or rivastigmine) and memantine (affects glutamate transmission) in conjunction with specialist advice from old-age psychiatry team (see p. 155).
- Low-dose haloperidol (e.g. 0.5 mg) can help control agitation and any accompanying delusions.
- Short-acting hypnotics, such as temazepam, can help insomnia.
- While on the ward, ensure adequate fluids, nutrition and treatment of constipation and any other reversible causes of incontinence.
- If possible, discharge home as soon as possible to avoid disorientating experience of admission.
- Involve the nearest relatives only.
- Referral to old-age psychiatry specialist dementia services.
 - **Progress.** This patient improved considerably after a few days in hospital with care from a multidisciplinary team. Her daughter lived fairly near so she was able with the therapist to arrange for aids at home to allow independent living. This patient was assessed by the psychogeriatrician who thought her dementia symptoms might well be related to her depression (pseudodementia) following the death of her husband. She was started on citalopram (an SSRI) 8 mg daily, with some improvement. She returned home, but requires continual supervision.

DELIRIUM TREMENS (DT)

Delirium tremens is the most severe form of alcohol withdrawal syndrome and is a medical emergency because of major complications that can arise.

It often occurs on the second or third day after admission, due to suddenly stopping drinking, although it can occur after a significant reduction in drinking in those who are highly alcohol dependent.

Case history

A 49-year-old man was admitted via A&E to the orthopaedic ward having had a fall and fracturing his pelvis. On the third day after admission he became disorientated and restless with visual hallucinations. The orthopaedic SHO wants your advice.

A full history elicits that he had been a heavy drinker for 10 or more years and obviously has had no alcohol since the fall. You think he has DTs – particularly as he has had a similar episode in the past.

Remember

Heavy drinkers under-report and conceal alcohol consumption.

The problem is suggested by:

- Regular medical presentations
- Injuries/falls
- Anxiety/depression/self-harm
- Marital/family/financial/legal difficulties.

What are the clinical features of DTs?

- Coarse tremor (which may affect the whole body)
- Disorientation in place and time
- Anxiety (often severe)
- Motor restlessness
- Nausea and/or diarrhoea
- Insomnia
- Nightmares
- Excessive sympathetic drive:
 - Sweating
 - Tachycardia
 - Hypertension
 - Low-grade fever
- Reduced attention
- Illusions: visual
- Hallucinations: classically visual and frightening, but may be tactile or auditory; small animals (insects, spiders, rats) advance menacingly towards and over the patient
- Persecutory delusions
- Convulsions in severe cases.

Remember

Complications of DTs

- Co-morbid illness or trauma (infection, dehydration, head injury)
- Hypoglycaemia
- Electrolyte disturbances (sodium, potassium, magnesium)
- Convulsions
- Coma
- Death.

Investigations

- Serum urea and electrolytes (especially hypokalaemia)
- Calcium and magnesium
- Gamma glutamyl transpeptidase (raised)
- Aspartate transferase
- Bilirubin
- Glucose
- Haemoglobin
- Mean corpuscular volume (raised)
- Mid-stream urine
- If necessary, appropriate X-rays to exclude infection (CXR) and trauma (CT brain scan if indicated: ?subdural)

How would you treat DTs?

- Admit the patient to an acute medical bed.
- General measures (see Delirium, p. 517).
- Particularly treat electrolyte and fluid imbalances.
- Treat any co-morbid disorder.
- Oral thiamine 200 mg daily even in the absence of Wernicke–Korsakoff encephalopathy, the specific signs of which can be missed in the presence of severe withdrawal symptoms. Treatment must be given early if long-term dementia is to be prevented.
- Parenteral high-dose thiamine is necessary in the presence of a thiamine-related encephalopathy.

Information

Wernicke–Korsakoff syndrome

Acute confusion, ocular palsies and nystagmus, and ataxic gait leading to chronic short-term memory loss and confabulation.

Specific drug therapy

- Follow a protocol if your hospital has one.
- Oral treatment is preferred unless the patient is severely distressed and disturbed. Doses suggested below may not be adequate to control the initial condition, and more may be required:
 - Diazepam 10 mg \times 4 daily orally *or*
 - Chlordiazepoxide 20 mg \times 4 daily orally.
- Chlormethiazole capsules should be avoided because of problems with dependence and adverse effects.
- Doses of chlordiazepoxide up to 200 mg spread over the first 24 hours may be required initially in uncontrolled, severe, life endangering withdrawal with fits. The patient must be monitored constantly with resuscitation facilities available.
- Prophylactic anti-convulsants (e.g. carbamazepine 200 mg \times 2 daily) should be given when there is a previous history of withdrawal convulsions or if the current presentation has been complicated by fits.
 - *Progress.* This patient improved after 3 days of diazepam treatment and the dose of the medication was tapered to nothing over the next 7 days. More gradual tapering is required in a patient with a history of convulsions, with a longer period (e.g. 3 months) on anti-convulsants. He was discharged from hospital with provision of long-term care arranged.

Long-term care

This primarily involves maintaining abstinence from alcohol. Referral to alcohol support agencies requires individual motivation. Acamprosate has been shown to be helpful in reducing craving in conjunction with support from addiction services or group therapy. Those with concurrent psychological problems (e.g. depression, psychosis) require psychiatric referral. This patient remains abstinent and still attends group therapy.

DEPRESSION

See also p. 159.

Depressive illness is common but often undetected or inadequately treated (see [Information](#) box, below). The central symptom is usually low mood. Associated symptoms reflecting effects on an individual's behaviour, thoughts, perceptions and cognition become more marked as the severity of the condition increases.

Whereas much depressive illness has an insidious onset and never reaches the attention of acute medical or specialist services, up to one-third of physically ill patients attending hospital have depressive symptoms.

In patients presenting acutely, depression can be associated with:

Information

Depressive illness can be missed in medical patients for the following reasons:

Information (continued)

- Depression considered 'understandable' in physically unwell
- Symptoms of depression attributed entirely to underlying medical condition
- Negative attitude to diagnosis of depression and reluctance to report symptoms
- Limited opportunity to discuss emotional issues in a medical setting

- Suicide attempt or deliberate self-harm (see p. 533)
- Concurrent physical illness (particularly chronic, painful, life-threatening or disfiguring)
- Unpleasant and demanding treatment for physical illness
- Destabilisation of a chronic condition, exacerbation of physical symptoms or excessive functional impairment
- Medical treatment refusal or poor compliance
- Weight loss, poor nutrition, self-neglect or unusual behaviour (e.g. heavy drinking)
- Increased somatic concern and unexplained physical symptoms.

Case history

A 66-year-old woman is admitted to a medical assessment ward for investigation of anaemia which had made her breathless and tired so that she was unable to cope on her own. Her husband died 6 months previously. The ward nurses have noted that she has been despondent, reluctant to care for herself and her nutritional intake has been poor. You suspect she may be depressed.

Information

Depression can be broadly categorised:

- Mild: low mood often associated with anxiety symptoms
- Moderate: increasingly low mood, depressive thinking (e.g. suicidal) with biological symptoms (sleep disturbance with early morning waking, mood worse in the morning, reduced appetite, weight and libido)
- Severe: more intense low mood, suicidal thoughts with development of psychotic symptoms, including delusions and hallucinations (most often associated with suicide)

How would you assess this case?

Investigations

- Full blood screen, including FBC, U&Es, creatinine (eGFR), thyroid function tests, liver function tests, serum calcium
 - A CXR may also be helpful
- Accurate diagnosis requires a detailed history, with a reliable corroborative account if possible, and mental state examination.
 - Factors that increase vulnerability to develop depression:
 - Previous history of depression
 - Family history of depression or suicide
 - Stress/life events particularly with separation or loss
 - Social isolation or adversity
 - Physical illness and its treatment
 - Medication that can cause depression
 - Alcohol/substance misuse.

Information

Assessment of mental state

Summary of the key areas of observation and enquiry:

- **Appearance/behaviour:** general state of health, self-care, facial expression, eye contact, rapport, cooperation, posture and movement
- **Speech:** rate, tone, quantity, volume, spontaneity and form
- **Mood:**
 - Sustained disturbance: depressed, elated, anxious, irritable
 - Reactivity: reduced 'blunted', increased 'labile'
 - Congruity: appropriateness to circumstances or theme of discussion
- **Thoughts:**
 - Preoccupations, predominant concerns
 - Mood-congruent ideas (e.g. suicidal)
 - Delusions: abnormal unshakeable beliefs inconsistent with sociocultural context
- **Perceptions:** auditory or visual hallucinations (a perception in the absence of a stimulus), presence of which may be suggested by abnormalities of general behaviour
- **Cognitive assessment** (see [Information](#) box, p. 525)
- **Insight:** recognition and attribution of illness/awareness of merits of treatment

Differential diagnosis

- Dementia
- Delirium

- Alcohol or substance misuse
- Chronic dysthymia
- Grief (normal or pathological).

How do you identify a severe case?

In moderate to severe depression, mental state examination may reveal:

- Depressed facial appearance, tearfulness, reduced expression, poor eye contact, retardation of movement or agitation.
- Speech: may be slow and impoverished.
- Persistent, pervasive low mood worse in the morning, anhedonia (loss of interest in pleasure), abulia (inability to make decisions), reduced motivation or energy. *Note:* these complaints are not usually attributable to physical illness alone – psychologically healthy people often cope resiliently with physical illness.
- Suicidal thoughts may be present and should always be enquired for and explored carefully:
 - Have you had any desperate thoughts?
 - Do you feel that life is not worth living?

Biological symptoms are often present. You should ask about feelings of hopelessness (often associated with suicidal contemplation). Other mood-congruent thoughts that might be present include pessimism, feelings of guilt, worthlessness, self-reproach, persecution, impoverishment. In severe depression thoughts can reach delusional intensity and may be associated with perceptual abnormalities, e.g. condemnatory auditory hallucinations. Tests of cognitive function may be poorly performed due to impaired memory and concentration. In the elderly with fragile but intact cognitive function severe depression may suggest a dementia ('depressive pseudodementia').

- **Diagnosis.** Moderate depression.

How would you manage this case?

- Exclude organic cause: this patient has an anaemia. Investigations show an Hb of 76 g/L, MCV 101, ESR 31 mm/hour, white cell count 4200.
 - **Diagnosis:** A macrocytic anaemia which is probably due to her poor nutritional state and likely to be due to folate deficiency. You do not want to treat her with folate until you have excluded B₁₂ deficiency.
 - The laboratory say that the serum levels will be available tomorrow, and when they arrive they show a serum B12 of 150 pmol/L, a serum folate of 6 nmol/L and a red cell folate of 70 µg/L, indicating **folate deficiency**. You start her on folic acid 5 mg daily with regular blood monitoring.
- Consider other possible organic causes of depressive symptoms (see **Information** box, below).
- Specific management depends on the severity:
 - Mild depression may respond to counselling and attempts to resolve problems leading to depression.
 - Mild to moderate depression can respond well to cognitive behavioural therapy, which requires time and available resources.
 - Moderate to severe depression is more likely to present and be detected acutely and often responds well to medication.
- Establish if the patient is at risk (see p. 525).
- Refer to psychiatric team but explain this to the patient first.

- Assess capacity if patient is refusing treatment.
- Psychiatric treatment can usually be managed by the liaison team on the medical ward: this is preferable if medical problems require treatment. A psychiatric nurse is required to observe the patient.
- The patient will require regular review.
- Psychiatric treatment or admission using the Mental Health Act is considered on the basis of severity and risk.
- Identify aftercare support from family or professionals having discussed this with the patient.
- Inform her primary care physician.

Information

Organic causes of depressive symptoms

- **Endocrine:**
 - Hypothyroidism
 - Cushing's syndrome
 - Hyperparathyroidism
 - Addison's disease
 - Hypercalcaemia
- **Infections:**
 - Viral illness
 - Hepatitis
 - HIV
- **Metabolic:**
 - Anaemia (particularly vitamin B₁₂ and iron deficient)
 - Renal disease
 - Cancer
- **Neurological:**
 - MS
 - Brain tumour
 - Parkinson's disease
 - Post-stroke
 - Dementias
- **Drugs** (many drugs have the potential to cause depressive symptoms: check data sheet). Examples include:
 - Steroids
 - Anti-hypertensives, beta blockers, digoxin
 - L-dopa, methyldopa
 - Cimetidine, metoclopramide
 - Aminophylline, theophylline
 - Regular use of stimulants

What medication would you consider and how would you begin treatment?

When prescribing anti-depressants:

- A psychiatric opinion is usually obtained.
- Medication is most effective in moderate and severe depression.

- Compliance is essential and enhanced by good communication. Good prescribing practice includes explanation of:
 - The diagnosis
 - The likelihood of response to treatment (around two-thirds respond well)
 - Common side effects, which often precede benefits
 - Delay of 2–3 weeks before therapeutic effect
 - Anti-depressants are not addictive (a common misconception).
- Older tricyclic anti-depressants (TCAs) have proven efficacy but significant side effects (e.g. anti-muscarinic, postural hypotension, cardiotoxic in overdose) and have largely been superseded by newer drugs. TCAs are still useful if newer agents aren't tolerated, sedation is desirable or if the patient has had a previous effective response. Avoid prescribing large quantities for outpatients and on discharge.
- Most commonly prescribed of newer anti-depressants are selective serotonin reuptake inhibitors (SSRIs), which can cause nausea but in general are better tolerated, cause fewer problematic interactions with other drugs and are less toxic in overdose.
- Difficult to predict which anti-depressant will be best tolerated in view of range of side effects and significant individual variation.
- Elderly patients often require lower starting dose and more gradual dose increase.
- As a general rule, treatment should continue for at least 6 months after recovery from acute episode.
 - **Progress.** This patient's depression responded to a mixture of bereavement counselling and drug therapy with an SSRI (escitalopram 10 mg daily). Her anaemia was due to dietary folate deficiency and responded well to treatment with oral folic acid, which was continued at home. She is being regularly seen by her GP and Hb levels checked. She is still on escitalopram.

Remember

- Severe depression can be life endangering (e.g. acutely suicidal, not eating or drinking)
- Refer to the psychiatric team, who may consider the use of emergency ECT treatment.

SUICIDE AND DELIBERATE SELF-HARM (DSH)

Patients presenting to hospital having attempted self-harm comprise around 10% of acute medical admissions. The most common method is drug overdose, which is associated with recent alcohol consumption in up to 50% of cases.

The majority of deliberate self-harm (DSH) does not represent a serious suicide attempt. Motivations include:

- Escape from overwhelming stress
- To effect a change in personal circumstances ('cry for help')
- Wish to die: serious suicidal intent is evident in up to one-fifth of DSH presentations.

Many of the components of the assessment of deliberate self-harm can be applied to patients who describe having 'suicidal thoughts'.

Case history

You are called to see a 24-year-old woman, accompanied by a friend who called an ambulance to bring the patient to A&E. The woman is tearful, smells of alcohol and says that she took a handful of paracetamol 4 h previously after a violent argument with her boyfriend. She tells you that her mother died 3 months ago and that she wants to join her. She has seen her doctor recently complaining of poor sleep.

Remember

- Dependants might be at risk (e.g. young children at home): inform social worker if necessary
- Some hospitals have dedicated staff who assess all patients. In these situations your task is to identify those who are in need of immediate attention or treatment.

How would you manage this case of deliberate self-harm?

- Examine the patient, check conscious level (GCS - 15), respiratory rate (15/min), blood pressure (104/72).
- Attend to immediate medical requirements (overdose, see p. 396). Most patients will be admitted to hospital after overdose for specific treatment or observation. Patients may underestimate or understate the number of tablets taken.
- When medical condition is stable, interview if possible with collateral history from reliable informants aiming to:

1. Identify mental illness

- Most completed suicides are associated with a psychiatric diagnosis, most often a depressive illness (see p. 528). Many suicide victims have seen their doctor in the preceding weeks.
- Conversely, clear psychiatric illness is evident in less than one-third of DSH presentations. Most occur after a 'life event', with up to half following a relationship problem.
- Most common diagnoses include depression, alcohol dependence, personality disorders (borderline, anti-social).

2. Detect patients at risk of completed suicide

- Serious suicide attempts form a minority of DSH presentations but individuals who harm themselves have a greatly increased risk of suicide compared to the general population.
- A high proportion of suicide victims have a previous history of DSH.
- An indication of risk should be documented in the notes with an appropriate plan of action.

Information

Features associated with increased suicide risk:

- Demographic: socially isolated (divorced, widowed, never married); male (rates in young men increasing steeply); older age, minority groups (e.g. young Asian women); unemployed; low socioeconomic class; certain professions (doctors, dentists, vets, farmers); individuals with access to means (drug users, gun owners)
- The attempt:
 - Planning: taking care of affairs (cancelled appointments, final acts, e.g. suicide note – the content of which can be helpful)
 - Circumstances: performed in isolation, steps to avoid detection
 - Method: violent, severe OD or believed likely to be lethal
- The history: present or previous psychiatric diagnosis (particularly depression, schizophrenia), recent hospital discharge, previous DSH, recent life event (e.g. bereavement, retirement, divorce), physical illness (chronic painful illness, CNS disorders (MS, epilepsy), cancer, HIV), family history of psychiatric illness/suicide, alcohol/drug misuse, impulsive personality
- The mental state: agitation, depressed mood, suicidal thoughts, hopelessness, delusions, hallucinations, insight in early schizophrenia

3. Explore suicidal thoughts

- Never avoid detailed but tactful questions concerning suicidal ideas and intentions.
- Responses need to be assessed in the context of the overall presentation, especially if the patient is unforthcoming.
- Establish the patient's thoughts about the episode of self-harm.
- Find out if the patient wishes to die: ask questions to assess underlying mental state, e.g.:
 - How does the patient see the future?
 - Does the patient see life as completely hopeless?
 - Does the patient feel he/she would be better off dead?
- Assess plans for further attempts: method, circumstances.
- Identify protective factors: reasons for not wishing to die, e.g. change in circumstances, family, dependants.

4. Identify means of preventing recurrence

The most significant factor predictive of repetition is the number of previous episodes. Assess:

- Current and previous coping resources
- Level of support: identify important relationships
- Possible precipitants (current problems, recent events) and means of addressing them.
- Alternative methods of dealing with distress.

Further management: psychiatric liaison referral

- Many hospitals have dedicated staff to assess all deliberate self-harm presentations in liaison with the psychiatric team. Learn to recognise individuals in need of immediate attention or treatment.
- Most patients do not require further psychiatric intervention.
- If a significant psychiatric disorder is identified, management can be initiated as an inpatient or outpatient in communication with the patient's doctor.
- High-risk cases or those with severe symptoms will require psychiatric admission – if necessary using compulsory detention. Level of risk and nursing observation required should be communicated and documented.

Difficult management problems

1. Repeated presenters (e.g. self-laceration, overdose, actual or threatened)

- Behaviour often associated with personality-related vulnerabilities (e.g. borderline personality), dysfunctional coping and intermittent stress in the absence of other clear psychiatric diagnosis.
- A planned, consistent multidisciplinary response coordinated through the psychiatric team can sometimes help provide containment.
- Reduction in the maladaptive expression of distress may occur with support from a key worker, counselling, psychotherapy or enhanced social support.
- Occasional, psychiatric crisis admissions may be required but these should be kept to a minimum in favour of longer-term strategies.
- Low-dose anti-psychotic medication may help to reduce arousal and subjective distress, avoiding prescriptions for large quantities and identifying a care professional or other reliable, willing carer to help supervise the medication initially if required.

2. Refusal of medical treatment

- Involve senior colleague and/or psychiatrist (to determine if mental disorder impairs capacity).
- Explain clearly the risks of not having treatment.
- Assess capacity to make informed decision and record it (see **Information box**, below).
- If treatment is considered necessary, attempt persuasion/negotiation, if possible including a friend or relative the patient trusts.
- Continue trying to gain the patient's trust, explaining merits of treatment and risks of refusal. A patient who is frightened, angry or presenting in crisis may choose to cooperate as his/her distress settles.
- If the patient has capacity and refuses treatment, a second opinion from a senior is advisable.
- It is essential that discussions with the patient, management decisions and their reasons are clearly documented in detail and discussed with a senior colleague.
- The Mental Health Act can be used to detain a patient who is refusing medical treatment in hospital if the patient is exhibiting symptoms of mental disorder that places their health, safety or that of others at risk and provides for the administration of treatment for a mental disorder that might be impairing a patient's capacity to decide on their medical treatment.

Information

Assessing capacity to withhold consent to examination, investigation or treatment

- Adults are presumed competent to refuse medical advice and treatment
- Decisions with more serious implications require greater capacity
- A patient lacks capacity if some impairment or disturbance of mental functioning causes inability to decide whether to consent to or refuse treatment, which is determined by:
 - Inability to comprehend and retain information on indications and benefits of proposed treatment and in particular the possible risks of refusing it
 - Being incapable of weighing up the information in order to arrive at a decision
- Temporary incapacity (e.g. due to head injury, altered mood, alcohol) may permit essential life-saving treatment without consent

3. Patients unwilling to remain in hospital for further assessment

- The patient's capacity to make this decision should be documented.
- If considered at risk, appropriate staff should attempt to detain in hospital under common law to permit an urgent mental health assessment by a psychiatrist and approved social worker. Reasons relating to the patient's behaviour, mental state and possible risks should be carefully documented.

4. Intoxicated or violent patients

- The assistance of hospital security or the police might be necessary.
- Assessment will be more productive if the patient is given time to sober up (in which case the behaviour may completely settle), as long as the patient or others are not put at risk.
- Consider psychiatric opinion if an underlying psychiatric disorder is thought likely.

Remember

Enforced physical treatment is given under common law and is not sanctioned by use of the Mental Health Act. Decision to go ahead depends on consideration of:

- Patient's capacity to refuse treatment
- Reasonable professional practice and a doctor's duty of care to the patient
- Necessity of the treatment to save life, prevent a serious incident or a deterioration in health
- Decision to treat being in the patient's best interests.

- **Progress.** This patient had taken approximately 20 tablets of paracetamol (10 g) and was given N-acetylcysteine intravenously (p. 401) and her liver function remained normal. This was her first episode of DSH and she realised the seriousness of what she had done and the necessity for future counselling.

Further reading

Hewson B. The law on managing patients who deliberately harm themselves and refuse treatment. *British Medical Journal* 1999; **319**: 905–907.

ACUTE ANXIETY

Case history (1)

You are called to the A&E to see a breathless young woman. She is acutely distressed and breathing rapidly. She feels light-headed and has paraesthesiae in her hands and feet.

Differential diagnoses such as a respiratory emergency (e.g. asthma, pulmonary embolus, and pneumothorax) must first be excluded (p. 325). Panic attack (see also p. 332) is suggested by:

- Extreme fear
- Subjective complaint of difficulty breathing in rather than out
- Respiratory alkalosis (causing tetany and relative hypocalcaemia)
- Arterial blood gases will show hypocapnia but normal oxygen levels
- Sweating
- Emotional trigger (shock)
- Environmental trigger (crowd phobia).

Management

Hyperventilation is best treated by re-breathing into a paper bag in order to increase $p\text{CO}_2$. However, this did not help this young woman and a minor tranquilliser was given (diazepam 5 mg orally). Lorazepam 1–2 mg, orally or IM is an alternative; this can be repeated 1 h later if necessary. She was sent home on diazepam and told to see her own doctor urgently for possible counselling.

Case history (2)

The nursing staff inform you that a 55-year-old man is refusing to have any more haemodialysis, having just started this treatment. A phobic reaction to dialysis is suggested by avoidance, abnormal fear and sympathetic over-drive, during dialysis or talking about it. Depressive illness is a common association of anxiety and should always be excluded (see p. 333). These phobias are also common in oncology (vomit phobia with chemotherapy).

How would you manage this patient?

- Support and sympathy with explanation of the phobia.
- Minor tranquilliser (see above) short term only: up to 2 weeks of diazepam 5 mg \times 3 daily (long-half-life drugs are better).
- Ask a psychologist to consider graded exposure therapy.
- A selective serotonin reuptake inhibitor (sertraline, citalopram, paroxetine, fluoxetine) is often required in the presence of co-morbid depressive illness.

Information

Patients can be educated about panic attacks and how to prevent them when better: (seek behaviour therapy for phobias) and the use of a paper bag during an attack.

What are the physical symptoms and signs of anxiety?

- Dilated pupils
- Photosensitivity: patient might be wearing dark glasses
- Phonosensitivity: patient cannot bear any noise
- Dry mouth
- Flushed face and neck
- Sweating
- Hyperventilation
- Associated hypocapnia and respiratory alkalosis: causing relative hypocalcaemia (tingling or numbness) in extremities and face, light-headedness and tetany (see p. 333)
- Tachycardia (pulse may be as high as 140 bpm)
- Nausea
- Diarrhoea
- Frequency of micturition
- Increased muscle tension.

What are the psychological symptoms of anxiety?

- Excessive fear
- Derealisation (patient feels that the environment is less real and solid, with a feeling of detachment)
- Fear of collapse
- Catastrophic thinking ('I'm about to die from a heart attack').

Always look for the following associations

- Phobias: abnormal fear and avoidance of particular situations or things
- Depressive illness (see p. 528)
- Obsessive-compulsive disorder: repetitive ruminations that are inconsistent with the personality, along with repeated behaviours; checking excessively or hand-washing because of fears of germs.
 - **Progress.** This man settled quickly with counselling and 5 mg of diazepam. He subsequently continued dialysis without any problems.

Further reading

Tyrer P, Baldwin D Generalised anxiety disorder. *Lancet* 2006; **368**: 2156–2166.

OPIATE DEPENDENCE

Drugs in this group include: diamorphine (heroin), morphine, pethidine, methadone, dihydrocodeine and buprenorphine.

Effects of opiate use

- Euphoria
- Analgesia
- Relaxation
- Drowsiness.

Heroin addicts are 16 times more likely to die than individuals of equivalent age, chiefly as a result of overdose. They frequently present in the acute hospital setting.

Case history (1)

You are called to see a 23-year-old man admitted 24 h previously following a road traffic accident. He is verbally abusing nursing staff and wants to leave against medical advice. He is demanding methadone, stating that he is a **heroin addict**.

How would you assess this man?

- Attempt to defuse the situation and prevent an escalation of disturbed behaviour.
- Take history of drug use including each drug taken, amount and route.
- Obtain information from other sources:
 - Previously or currently attended drug support agencies if patient admits to having received help. They may be able to tell you if the patient has a regular prescription for methadone.
 - Corroborative history from reliable other informant with patient's consent.
- Examine for evidence of opiate use: withdrawal symptoms begin within 12 h of last use and increase in severity over the first 48 h. With longer-acting opioids such as methadone, onset of withdrawal symptoms can be delayed and their duration increased. Opiate withdrawal that is uncomplicated by other drugs is subjectively unpleasant but not life-threatening, and can present with:
 - Agitation
 - Anxiety
 - Low mood
 - Restlessness
 - Tachycardia
 - Sweating
 - 'Goose flesh'
 - Dilated pupils
 - Yawning

- Sneezing
- Vomiting
- Lacrimation
- Rhinorrhoea.
- Look for evidence of recent drug use, e.g. needle marks, phlebitis, skin abscesses. Subjective complaints include craving, poor sleep (which can last months), abdominal cramps, nausea, diarrhoea, musculoskeletal pain.

How would you investigate this patient?

- Send urine for drug screen.
- Infection screen (risk of hepatitis B, C, HIV).

How would you manage and treat this patient?

Prescribing methadone

- Oral methadone mixture should be given if you are satisfied a significant habit exists, and this is confirmed by reliable sources or objective evidence of use or withdrawal symptoms.
- If possible, seek advice from local specialist drug unit.
- There are published guidelines on clinical management of drug use and dependence – a copy should be available in the hospital pharmacy.
- Any registered medical practitioner can prescribe methadone.
- Methadone tablets should not generally be prescribed because of their potential for misuse.
- Dose required to control withdrawal can be carefully titrated in hospital. Start at low dose of methadone, e.g. 10 mL (1 mg per 1 mL mixture). Further 10 mL at 4-hourly intervals is used until objective signs of withdrawal are controlled. Establish daily requirement.
- Doses above 40 mL (40 mg) daily should only be taken if there is reliable information that the patient has been receiving higher regular prescription, but even in this case dose should be gradually titrated upwards.

Remember

Avoid high doses. Methadone overdose causes respiratory arrest – patients can overstate their requirements and physical tolerance to opiates can change quickly.

Symptomatic treatment of withdrawal symptoms may be indicated and includes:

- Ibuprofen for pain.
- Loperamide for diarrhoea.
- Patients may demand more methadone than required to control withdrawal symptoms in order to promote sleep. This should be avoided. Short-term use of hypnotic medication is an alternative. Diazepam also helps muscle spasm and anxiety.
- Observe for evidence of withdrawal from other drugs, e.g.:
 - Alcohol: DTs (see p. 526)
 - Benzodiazepines: risk of convulsions.

- Comorbid psychiatric disorder can be present:
 - Depressive illness (see p. 528)
 - Psychotic symptoms (if polydrug use includes stimulants or hallucinogenic drugs).

When condition stable

Gradually reduce methadone by 10% per day if aiming for abstinence. The patient wishes to remain on methadone in the longer term and was already receiving regular prescription prior to admission. He requests referral to local drug support service. The reduction regimen may require some flexibility to promote cooperation.

Remember

Patients should be warned of the risks even of relatively low doses of methadone and be cautioned about its safe keeping, particularly if there are children at home (5–10 mL could be lethal for a child).

- **Progress.** On discharge, as drug service support is required, arrange planned transfer of care and be specific about who will prescribe and when. The patient's doctor should be informed and may be willing to prescribe. Avoid giving large prescriptions. Methadone should generally be prescribed for collection on a daily basis, but drug services can advise on this. This patient continues on methadone supplied by the local drug support service.

Case history (2)

A young man is rushed to A&E in a comatose state. His girlfriend tells you he used heroin after an abstinence of 4 weeks.

How do you proceed?

Urgent cardiorespiratory support should be available.

- Assess evidence of opiate toxicity (an acute medical emergency):
 - Conscious level (Glasgow Coma Scale - 13)
 - Respiratory depression - 12 bpm
 - Bradycardia - 52/min
 - Miosis - present
 - Hypothermia. - 36.4°.
- Examine for other causes of impaired consciousness (e.g. head injury).
- Administer opiate antagonist naloxone (0.8–2 mg): IV naloxone has a high affinity for opiate receptors and reverses the signs of toxicity by displacing ingested opiates. Life-threatening symptoms may recur in view of the relatively short half-life (minutes) of naloxone, which may need to be re-administered depending on the half-life of the opiate taken (e.g. half-life of methadone is over 24 h).

Heroin overdose, causing life-threatening respiratory depression, can occur after a period of abstinence as physical tolerance is reduced.

Remember

All patients need to be monitored in hospital for at least 24 h even if they make a brisk recovery.

- **Progress.** This patient made a rapid recovery with the use of repeated naloxone and he agreed to be referred back to the Drug Dependency Unit.

THE DISTURBED PATIENT

A behaviourally disturbed patient is often distressed and frightened by their subjective experiences or the circumstances in which they find themselves. The behaviour may place the individual or others at risk.

Typical presentations:

- Agitation and restlessness
- Over-activity
- Communication of distress, e.g. self-injury or mutilation, threats to harm self
- Fluctuating and unpredictable behaviour
- Intimidating, defensive or oversensitive behaviour
- Verbally loud, aggressive or violent conduct.

Underlying causes of disturbed behaviour include:

1. Organic mental disorders

- Dementia: patients can be restless, aggressive and may wander because of disorientation. May be exaggerated by coexistent physical conditions, e.g. acute infection, constipation.
- Delirium (see p. 515): arising from a number of causes and commonly associated with disturbed behaviour due to misinterpretation of surroundings. Conscious level is impaired, often with fearfulness, perceptual abnormalities (visual or auditory hallucination) and abnormal thinking (e.g. persecutory delusions).
- Epilepsy: ictal (e.g. temporal lobe) or post-ictal.

2. Other psychiatric disorders

- Major psychoses:
 - Schizophrenia: delusional thinking or abnormal sensory experience (e.g. auditory hallucination) may be driving behaviour.
 - Manic psychosis: elevation in mood can be associated with hyperactive and disorganised behaviour.
- Anxiety and depression (see pp. 538, 528): can be associated with agitation, restlessness and high arousal. Major depression is associated with suicidality and self-harm.

3. Substance use

Alcohol intoxication or withdrawal (see p. 526). Use of other drugs, e.g. stimulants, hallucinogenics, solvents.

4. Physical illness

Individuals may have a physical cause to explain their disturbed behaviour, e.g. chronic pain, side effects of medication.

5. Personality factors in the absence of physical or psychiatric disorder

Personality vulnerabilities or 'disorders' can give rise to several distinct patterns of problematic behaviour, which may be associated with circumstances, crises, stress or intoxication. This can include exaggerated propensities to express anger, violent, explosive or anti-social conduct or self-mutilating and cutting.

Case history

A young man walks into A&E. He is unkempt, preoccupied and suspicious. His behaviour is bizarre, disorganised and unpredictable. He has been argumentative and intimidating, causing distress to staff and other patients.

Management

- Aim to identify cause and take control of the situation.
- Of paramount concern is the safety of the patient, other patients, yourself and colleagues.
- Disturbed patients should be assessed in a safe area with adequate staff support (medical, nursing, security) and access to a panic alarm.
- Consider the possibility that the patient might be concealing a weapon.
- Specific management depends on the severity of the disturbed behaviour and the cause.
- Clues to the diagnosis can often be found by carefully observing an uncooperative patient even from a distance while awaiting staff support, e.g. impairment of the conscious level may suggest delirium, drug intoxication; a smell of alcohol may be apparent. A major psychotic mental illness may be suggested from the appearance, behaviour and speech, e.g. preoccupation, suspiciousness, over-activity, thought disorder, delusional ideas.
- Additional background information from reliable informants is invaluable but not always possible.

After an initial assessment of the situation, and with appropriate staff support: a further attempt to calm this patient should be made.

Use interpersonal skills/de-escalation

- Approach the patient in a non-confrontational manner, avoiding invasion of their personal space – disturbed patients may misinterpret their surroundings and the motives of others and whereas their behaviour can create fear in those around them they are often defensive and frightened themselves. The likelihood of cooperation is enhanced if the patient feels safe.
- Clear communication with sensitive statements and questions is often helpful.
- Ask the patient what he/she wants; listen and offer advice and reassurance.

- Attempt to interview the patient in a safe, relaxed setting.
- If initial attempts to engage the patient fail, providing the situation has not escalated, give the patient some space and time before trying again. Make sure the patient is appropriately observed. The time can be used to consider alternative management.

Patient remains uncooperative

An uncooperative patient whose behaviour is of concern and suggests a mental health problem will require an urgent mental health assessment. An approved 'clinician' – under the Mental Health Act (often the duty psychiatrist) – is required to sign a medical recommendation that the patient be detained on mental health grounds. If this is appropriate, the patient will be transferred to the psychiatric team. Should the patient's behaviour be considered to present a risk to themselves or others before this can be completed, the use of restraint and possibly medication (see below) under common law should be considered. The reasons for this course of action should be clearly documented and suitable staff should be available.

Following implementation of Mental Health Act

As the patient's behaviour remains disturbed and is a risk to himself and others, safe restraint should be used as a coordinated response by suitably trained nursing staff. This involves sufficient numbers so that at least one can hold each limb, with two nurses taking responsibility for giving the medication.

Medication

- Reduction in arousal can be achieved by a carefully planned regimen of anti-psychotic medication, preferably given orally and in liquid form in the first instance.
- Before deciding on intramuscular medication, all non-invasive measures to calm the patient and secure cooperation should be attempted. Even patients who present as highly disturbed initially may agree to take oral medication when it becomes clear that the situation is under control.
- Giving intramuscular medication to a potentially resistive and aroused patient is not without risk, which must be outweighed by risks of inaction and clearly documented.
- Resuscitation equipment must be available.
- A patient receiving intramuscular medication under restraint should be held in the prone position to protect the airway. The patient is released gently when signs of relaxation and calming become evident and placed under constant observation.
- The dose of anti-psychotic medication can be reduced by combination with a sedating benzodiazepine in the short term.
- Start at low doses and increase gradually depending on response. A suitable regime is:
 - Haloperidol 5 mg IM
 - Lorazepam 1–2 mg IM.
- Vital signs (pulse, temperature, blood pressure, conscious level) should be monitored every 15 min.
- While the behaviour continues to present a risk, the dose may be repeated at intervals of 30 min to 1 h until the patient is settled, subject to regular monitoring of vital signs.

Remember

Particular caution should be used in patients who have never received anti-psychotic medication previously ('neuroleptic naïve') because of the possibility of adverse effects such as a hypersensitivity reaction or acute dystonia.

When the patient is more settled

Further assessment can be carried out to establish an accurate diagnosis prior to starting regular treatment.

- **Progress.** This patient's doctor is eventually contacted and you are told that a diagnosis of schizophrenia was made 5 years ago. The patient had been well but the doctor said he had not attended the clinic (despite reminders) in the last 3 months and suspects he has run out of medication. He has been on olzapine 10 mg daily. This information is passed on to the psychiatric team who continue his management.

A SWOLLEN RED LEG

Case history

The A&E officer asks you to come and see a 50-year-old man who is unwell and has a red, swollen leg. He thinks he needs anticoagulation for a possible DVT.

On arrival you check if this was of sudden onset or a chronically swollen leg. You ask if there is a past history of DVT or whether there are any risk factors, such as a long car journey, air travel, immobility or a family history of clotting disorders. You also ask about any recent illness, e.g. heart failure, blood disorder.

What should you do next?

You do a full medical examination.

On examination the patient weighs 102 kg and has a temperature of 38°C. The leg is indeed red, swollen, hot and tender below the knee. You note a small ulcer on the medial side of the leg above the ankle. Dorsalis pedis pulse is palpable.

What is your diagnosis?

Cellulitis, probably due to streptococci gaining entry via the venous ulcer.

Differential diagnosis

- Deep vein thrombosis
- Ruptured Baker's cyst
- Lipodermatosclerosis
- Acute allergic contact dermatitis: e.g. to dressings
- Necrotising fasciitis: black necrotic areas within cellulitic area.

Information

Lipodermatosclerosis

- Hot, red and woody hard 'atrophic' skin
- Long-standing venous disease
- Can mimic cellulitis but the patient is well, there is no pyrexia, and it may be bilateral

Investigations

- Streptococcal titres: ASOT, ADB (anti-DNase B)
- Swab/blood cultures rarely helpful

How do you treat?

Penicillin V plus flucloxacillin 500 mg \times 4 daily, having ascertained that he is not allergic to penicillin. Oral therapy should be for 10–14 days. When the cellulitis is very severe, parenteral benzylpenicillin 1.2 g \times 4 daily and flucloxacillin 1 g \times 4 daily, i.e. 3 days' intravenous therapy should be given initially, followed by 10 days' oral therapy.

- **Progress.** The patient's leg improved with antibiotics and he was discharged after 3 days. He was given compression stockings for his venous hypertension. He was referred to a dietitian for advice on weight reduction.

Further reading

Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev* 2010; 6: CD004299.

Leg ulceration

Take a full history of associated diseases (diabetes mellitus, rheumatoid arthritis, past history of deep vein thrombosis, varicose veins, heart disease, hypertension, vasculitis, sickle cell, scleroderma).

Causes and signs

- Venous hypertension:
 - Ulcer: chronic and recurrent; site – internal malleolus
 - Oedema
 - Venous eczema
 - Skin discoloration: atrophie blanche (stellate scarring with telangiectasia), erythema, haemosiderin pigmentation
 - Skin texture: lipodermatosclerosis.
- Arterial disease:
 - Ulcer: punched out; site – often lateral or higher up on leg (painful)
 - Pulses: absent dorsalis pedis or posterior tibial
 - Cool leg.
- Vasculitis: non-blanching purpura.
- Neuropathic: sensory signs of decreased sensation present particularly over pressure areas on feet; common in diabetics.

Investigations

- General: FBC, U&Es, LFTs, autoantibodies (vasculitis), blood sugar, vitamin B₁₂, T Pallidum enzyme immunoassay (neuropathic ulcer)
- Venous: Doppler ultrasound – always perform before compression bandaging
- Arterial: Doppler ultrasound, digital subtraction angiography

Management

- **Venous ulcers:** elevation, exercise, compression dressings. Antibiotics if infected (always check Doppler pressures before considering compression as many ulcers have mixed venous and arterial aetiology). Adequate analgesia.
- **Arterial ulcers:** investigate arterial supply, dressings with NO compression. Adequate analgesia.
- **Vasculitic ulcers:** vasculitic screen, e.g. ANCA, ANA, rheumatoid factor.
- **Neuropathic ulcers:** keep ulcer clean and remove pressure or trauma from affected area.

Note: Operating on varicose veins rarely helps venous insufficiency problems – ‘re-plumbing’ of the veins is not possible.

Contact your hospital’s tissue viability nurse for assistance with dressings and compression bandaging and for arranging longer-term community nursing follow-up.

Information

Compression bandages

- Four-layer bandaging provides high levels of graduated compression with pressure decreasing up the leg
- 80% of ulcers can be healed within 6 months

ERYTHEMA NODOSUM

Erythema nodosum (EN) is a hypersensitivity reaction to various antigens (e.g. drugs, infectious agents and unknown antigens), producing an inflammation in the dermis and subcutaneous layer (panniculitis).

It presents with painful, tender, dusky blue red nodules, usually on the shins and lower limbs (Fig 17.1).

Case history

An unmarried 16-year-old Asian girl presents to an inner city A&E with her mother. She has painful red lumps on her shins and arthralgia. Walking has become painful. She is otherwise well, with no relevant previous medical history.

On examination she has tender, red/purple lumps on her shins. No other signs. A clinical picture was of erythema nodosum.

Make the diagnosis

- Spontaneous onset over days; evolution over a few days or weeks
- Single or multiple deep bruise-like nodules 1–10 cm diameter (better felt than seen)



Figure 17.1 Erythema nodosum.

- Tender and warm to touch
- Predominantly affecting limbs (shins or lower limbs)
- No age or sex limitation (but young females more common)
- Sometimes associated with arthralgia
- Always do a CXR looking for hilar lymphadenopathy or TB.

What is the cause?

- Drugs:
 - Oral contraceptives
 - Aspirin and other NSAIDs
 - Sulphonamides.
- Infection:
 - Streptococcal
 - Tuberculosis
 - Leprosy (patient from endemic area)
 - Chlamydia (rare).
- Sarcoidosis.
- Inflammatory bowel disease.
- Idiopathic (common).
- Pregnancy.

Initial treatment

- Aspirin 600 mg as required (unless the identified cause of the EN).
- Bed rest if severe.
- Tubigrip support bandages.
- If severe symptoms and/or cutaneous ulceration, use dapsone (up to 100 mg daily)/steroids (30 mg daily decreasing course).

Note: monitor for haemolytic anaemia and avoid dapsone if G6PD deficient.

When should she be referred?

- Recurrent or unresolving symptoms
- Ulceration
- Sarcoidosis/tuberculosis/leprosy/inflammatory bowel disease suspected
- Systemically unwell patient.
 - *Progress.* This girl went home with her mother, reassured that her illness would settle. After 7 days with occasional aspirin therapy she was much better and was able to restart school. Her chest X-ray showed hilar lymphadenopathy. With erythema nodosum this is characteristic of **sarcoidosis**.

She returned to the hospital after 6 months for a follow-up chest X-ray, which was normal.

URTICARIA AND ANGIO-OEDEMA

Urticaria or **hives** is characterised by short-lived dermal swelling (weals) anywhere on the body (Fig. 17.2). These usually itch and, except in some subtypes, resolve without bruising within 24 h (often within 10–20 min). They can form bizarre serpiginous or annular-shaped lesions. The latter show central clearing, not central necrosis as seen in erythema multiforme.

Angio-oedema is a deeper form of swelling affecting the dermis and subcutis, usually affecting the mucous membranes, e.g. eyes, lips, tongue, genitals, and much less commonly the larynx and gastrointestinal tract. It is generally not itchy but can be painful and disappears within 72 h. It may occur in isolation or with urticaria (45% cases).

The incidence of urticaria/angio-oedema is about 15% in a person's lifetime and both conditions are more common in atopics.



Figure 17.2 Urticaria.

Case history

A 22-year-old woman presents in A&E with a 6-hour history of a florid raised red rash all over the body. It is very itchy and distressing and has caused swelling around her eyes and her right hand. Previous medical history was of atopic eczema as a child and mild hay fever.

On examination she had red, raised weals all over her body and periorbital swelling.

- **Diagnosis.** Urticaria with angio-oedema.

Classification of urticarias

Acute

By definition this lasts < 6 weeks. Few cases have an identifiable allergen. They are IgE mediated. In the most severe form there is an anaphylactic reaction but this is fortunately very rare:

- Acute idiopathic urticaria and angio-oedema: accounts for > 90% of urticaria. A good history (not type 1 allergy testing) should exclude an allergic cause. Viral infections will sometimes set off an acute urticaria.
- Acute allergic: drug reactions, insect bites, foods (e.g. peanuts or seafood), can cause this type of reaction, as well as contact urticaria caused by, e.g. latex, tomatoes. A history of an almost immediate reaction (seconds to minutes) after contact with an allergen should alert one to this form.

Chronic

By definition if urticaria persists > 6 weeks. Only 2–4% cases have an identifiable cause and extensive investigation is not indicated. Some cases are autoimmune and functionally significant IgG (which acts against the high-affinity IgE receptors on mast cells) can be demonstrated in patient's serum. In a few patients an acute illness (hepatitis, brucellosis), focal sepsis (e.g. dental abscess), dermatophyte or parasitic infections can precipitate a reaction but this is very rare.

Physical

Reproducible wealing occurs in response to a specific physical stimulus, e.g. friction, pressure, cold, heat, water, sun. The diagnosis might be suspected from the patient's history or site of urticaria i.e. pressure sites in cases of dermatographism or delayed pressure urticaria.

General management

- Explanation of condition and likelihood of not identifying specific cause.
- Avoidance of non-specific factors, e.g. aspirin, NSAIDs, opiates.
- H₁ anti-histamines (non-sedating or combination of daytime non-sedating H₁ blockers and sedating H₁ blocker at night); 90% of cases will respond to a non-sedating anti-histamine.
- H₂ anti-histamines, e.g. cimetidine 400 mg × 2 daily.

- Immunotherapy:
 - Short-term: a short, 7-day course of oral prednisolone 30 mg daily may be given in A&E to quickly settle an attack (especially if angio-oedema prominent) while waiting for anti-histamines to work
 - Long-term: dapsone, corticosteroids, IV immunoglobulin, ciclosporin. For very severe cases, refer to dermatology department.

Preferred regimes if no contraindications

- Loratidine 10–20 mg daily or cetirizine 10–20 mg daily or fexofenadine 180 mg daily (all non-sedating anti-histamines).
- Sedative anti-histamines, e.g. hydroxyzine 25–50 mg at night.

Refer: to dermatology department if no response to anti-histamines.

Refer: to type 1 allergy clinic (usually different to dermatology) *only* if allergic urticaria is suspected from history.

Management of severe angio-oedema

See p. 409.

- Adrenaline (epinephrine): 1:1000 (1 mg/mL) IM. Adult dose 0.5–1.0 mL.
- IV chlorphenamine: 10–20 mg (max. 40 mg/24 h).
- IV hydrocortisone succinate: 100–300 mg.

Home (injectable adrenaline) pens

These should never be prescribed lightly and only after full investigation in an allergy clinic when relevant allergens have been proven and where a genuine anaphylactic reaction has occurred. They are most commonly used in those severely allergic to nuts. Injectable adrenaline pens are *not* appropriate for isolated severe cutaneous urticaria or angio-oedema.

Patients/parents need to attend an allergy clinic to be instructed in both when and how to use the pens and, indeed, how frequently if the first injection only gives temporary relief (two pens should be prescribed).

Adrenaline (epinephrine) 1 : 1000 (1 mg/mL) is available in pre-loaded injections to deliver a dose of 0.3 or 0.5 mg (adult) or 0.15 mg (paediatric) and injections should be carried out by the patient.

- **Progress.** This patient was given prednisolone 30 mg daily for 7 days and started on loratidine 20 mg daily. The nature of the complaint was explained to her; no specific antigen was identified. She was seen by her doctor after 4 days and was completely free of symptoms. She continued with loratidine for 1 month.

Hereditary angio-oedema (HAE)

Skin lesions may develop and laryngeal obstruction can occur. Lesions appear as deep swellings with associated enlarging oedematous borders that last up to 2–4 days. Urticaria does not occur as part of HAE. Patients generally suffer from recurrent attacks of painful angio-oedema, which can be precipitated by minor trauma, emotional upset, infections and temperature change. Involvement of the gastrointestinal tract can cause severe acute pain and simulate a surgical emergency. Recurrent abdominal pain occurs often and starts in childhood. HAE is inherited in an autosomal dominant fashion with either a functional or absolute deficiency of C1 esterase inhibitor (C1-INH). 80% of cases give a positive family history (e.g. of sudden death). Acquired forms are seen in SLE or lymphoma.

Remember

Hereditary angio-oedema (HAE)

Patients can develop laryngeal obstruction requiring urgent treatment.

Investigations

Two blood samples need to be sent for both absolute levels and functional assay of C1-INH (discuss with laboratory first). Only do this test in patients with recurrent angio-oedema who do not have urticaria. Refer all such patients to local immunologist/ dermatologist depending on local expertise.

Management

Patients are unresponsive to anti-histamines, which can exacerbate the condition, systemic steroids and adrenaline (epinephrine). Refer all patients for management: acute treatment of choice in A&E is intravenous (C1-INH) concentrates. If unavailable, fresh frozen plasma can be used. Most already diagnosed cases/families will know where local supplies of C1-INH are to be found. Icatibant (a bradykinin antagonist) and ecallantide (a kallikrein inhibitor) are also of benefit in acute attacks.

In adults, chronic treatment or 'prophylaxis' with attenuated androgens, e.g. stanozolol or danazol, is required if episodes are frequent.

Further reading

Morgan BP. Hereditary angioedema – therapies old and new. *N Engl J Med* 2010; **363**: 581–583 (and 513–22, 523–31, 532–41).

SUN-INDUCED RASH

Case history

A 24-year-old arrived in A&E with blisters on her face and arms. She had fallen asleep on the beach in the sun. She had applied factor 4 sunscreen and was surprised that she had developed an itchy rash. On examination she had papules and a few vesicles over the exposed areas.

Remember

- Always take a drug history in somebody who is photosensitive (e.g. doxycycline, amiodarone)
- Always keep SLE and porphyrias in mind for any photosensitivity case where diagnosis is not obvious.

What is the diagnosis?

This is **polymorphic light eruption**, which occurs in 10–20% of the population. The rash appears some hours after the exposure and can last for several hours or a few days following exposure. The rash may be papular or papulovesicular. This patient also had evidence of sunburn – remember, factor 4 does not protect for very long.

Differential diagnosis

Common

- Polymorphic light eruption
- Sunburn
- Sunscreen allergy leading to photocontact dermatitis (presents as eczema rather than papules/vesicles)
- Drug-induced photosensitive rash (eg doxycycline, amiodarone).

Rare

- Photosensitive eczema
- Lupus erythematosus (all forms)
- Porphyrias
- Actinic prurigo
- Solar urticaria (very rare) gives rise to a rash immediately after sun exposure.

Note: ‘prickly heat’ or ‘heat rash’(miliaria) are incorrect labels often given to polymorphic light eruption. This is an intensely itchy papular eruption in the flexures in hot humid conditions. It is due to blockage of the sweat ducts and does not require sun exposure and is also not on sun-exposed skin.

Information

UVA and UVB

- Medium wavelengths 280–310 nm (UVB): cause sunburn and long-term skin changes, e.g. ageing/cancer
- Long wavelengths 310–400 nm (UVA): do not cause sunburn (unless high doses through glass) but do cause photodermatoses. Also contribute to long-term skin damage
- Sunscreen preparations protect against UVB: the sun protection factor (SPF) number gives an indication of the amount of time that a person is protected against burning compared to unprotected skin. Most sunscreens also protect against UVA by utilising reflectants or chemical absorbers

Most sunscreens are insufficiently applied (and not reapplied after bathing) and so do not give the protection suggested by the SPF factor.

How would you treat this patient?

No treatment was necessary for this young woman because she was virtually asymptomatic. She was given a leaflet on sun exposure and told that her type of rash usually tended to improve over the summer period.

Refer: to dermatology department if condition is not controlled by use of sun block and advise to slowly increase sun exposure in spring/early summer.

If the rash becomes worse each year, consider desensitising with low-dose PUVA each spring or short bursts of oral prednisolone 30 mg daily for 1 week for an attack.

Further reading

Lehmann P. Sun exposed skin disease. *Clinics in Dermatol* 2011; **29**: 180–188.

GENERALISED RASH OR ERUPTION

Erythroderma means red skin. By definition, it is the term used when > 90% of the skin is involved. Erythroderma is not an extensive maculopapular rash.

Case history

A 63-year-old man presents in A&E unwell, shivering and red all over. He has suffered with chronic plaque psoriasis for 40 years and has been managed on topical therapy only. He smells of alcohol and admits to being a heavy drinker.

Examination reveals **erythroderma** and multiple tiny pustules over the trunk. He has a pyrexia of 39.5°C and is clinically dehydrated.

Clinical

Take a comprehensive history of onset, past history, previous skin disease, family history, medication, occupation and other systemic symptoms. These include chills, flu-like symptoms and itching and burning of the skin. A full skin examination, including nails, mouth, genitals, scalp and hair, should be performed, as well as a general examination of lymph nodes and organomegaly.

Differential diagnosis

- Eczema
- Psoriasis
- Drug eruption
- Idiopathic
- Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)
- Pemphigus foliaceus.

Are there any complications you should look out for?

Check for:

- High-output cardiac failure from increased blood flow
- Hypothermia from heat loss
- Fluid loss
- Hypoalbuminaemia

- Increased BMR, i.e. catabolic
- Capillary leak syndrome in very severe cases of psoriasis can give rise to ARDS (*Note*: this can be seen in severe drug rash).

Management

- Bed rest
- Rehydrate, plenty of fluids orally or IV
- Keep warm (space blankets)
- Moisturise the skin
- Refer all cases to dermatology urgently
- Regular (hourly) observations, e.g. blood pressure, pulse fluid input/output chart, core temperature, weight.

Investigate for cause and treat as appropriate according to primary skin disease.

Investigations

- FBC
- U&Es
- LFTs
- CXR
- Culture of blood, skin, urine, sputum if pyrexial
- Skin biopsy (later)

- **Progress.** This man was treated initially with intravenous glucose/saline with added potassium, then oral fluids. His core temperature fell to 37.2°, so he was kept warm with space blankets in a heated room.

He remained unwell for 2 weeks but then gradually improved.

PRURITUS

Differentiate whether there is a visible rash that is itchy or if there is 'normal looking' skin (with no rash other than scratch marks) that is itchy.

Case history

A 19-year-old white man presents with a 6-week history of an itchy skin which has been 'driving him mad' especially at night-time and he can't sleep. He is fed up with his doctor, who said he had scabies and has treated him four times with malathion without benefit. PMH/SH nil relevant. He had bad asthma as a child.

On examination he had multiple small red papules on trunk, around nipples, wrists, axillae and on the penis. These were accompanied by marked excoriations. No burrows were seen. A few lesions were seen on the soles of the feet.

- **Diagnosis. Scabies.** The diagnosis of scabies was made on clinical grounds. Burrows are not always present but the distribution of non-specific papules (occasionally vesicles) is highly suggestive. Sites commonly involved are axillae, nipples, penis, wrists, palms, soles and web spaces. The face/head is spared in adults. Scabies can be confirmed by skin scraping and microscopy. He lived with his girlfriend (who was unaffected) and had recently visited a prostitute, who may have been the source of infection.

Causes of pruritus

Diseases of the skin associated with pruritus:

- Eczema (Fig. 17.3)
- Scabies
- Urticaria
- Psoriasis
- Lichen planus
- Dermatitis herpetiformis
- Pemphigoid.

Systemic diseases associated with pruritus:

- Hypothyroidism
- Iron deficiency
- Advanced chronic kidney disease
- Liver disease (especially PBC and hepatitis C)
- Lymphoma/myeloproliferative disease
- Coeliac disease.

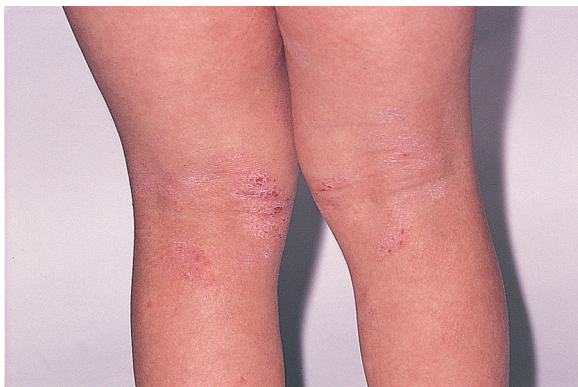


Figure 17.3 Eczema.

General management of urticaria

Treat primary skin disease. Refer to dermatology.

- Eczema: moisturisers and topical corticosteroids
- Psoriasis: tar, vitamin D₃ ointments, mild to moderate topical steroids, dithranol (causes staining)
- Urticaria: non-sedating anti-histamines (see p. 553)
- Lichen planus: superpotent topical steroids/oral steroids
- Systemic diseases: see individual disease for treatment.

Investigations

- Primary skin diseases: most cases can be diagnosed on clinical grounds but scrapings for direct microscopy (scabies), punch biopsy (+ immunofluorescence), serum IgE for atopic disease are helpful
- Systemic diseases: FBC, U&Es, LFTs, iron, folate, vitamin B₁₂, TFTs, autoimmune hepatitis screen, including mitochondrial antibodies, endomysial/gliadin antibodies. Consider serum Igs/protein electrophoresis/CXR in selected cases

Progress

- Scabies: malathion was given to him and his girlfriend. He was told to be careful in applying malathion all over his body, including crevices of his body and webs of his fingers. This should be washed off after 24 hours. Sexual contacts (if known), even if asymptomatic and no rash, should be given two treatments 7 days apart.
- Repeated scabies prescription leads to irritant dermatitis. Patients should be warned that the itching can go on for 1 month after successful treatment of scabies. Therefore give some crotamiton or topical steroid rather than further scabies prescription.

This patient's scabies, on this occasion, was treated successfully because he was meticulous in the application of malathion.

Further reading

Batchelor JM, Grindlay DJC, Williams HC. What's new in atopic eczema? An analysis of systematic reviews published in 2008 and 2009. *Clinical and Experimental Dermatology* 2010; **35**: 823–828.

Menter A, Korman NJ, Elmets CA et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6. *J Am Acad Dermatol* 2011; Feb 7 Epub.

CUTANEOUS ADVERSE DRUG REACTIONS (ADR)

The true incidence is unknown as many go unreported but the skin is the most commonly affected organ, involved in 30% of reported ADRs.

Pre-existing disease (SLE, CLL, HIV), advancing age (poly-pharmacy, reduced renal and hepatic clearance), sensitivity to other drugs (e.g. penicillins: 10% cross-reactivity with cephalosporins) can all increase susceptibility to the development of ADRs.

Case history (1)

A 24-year-old man developed a severe sore throat and a fever. He was seen by his doctor, who diagnosed a streptococcal sore throat and prescribed amoxicillin. Two days later he presented with a macropapular rash (Fig. 17.4).

On examination he was noted to have cervical lymphadenopathy and a small palpable spleen. Infectious mononucleosis was diagnosed with a monospot test and the amoxicillin was stopped.



Figure 17.4 Maculopapular rash following amoxicillin therapy in infectious mononucleosis.

Remember

Never use amoxicillin in a patient unless glandular fever has been excluded.

Case history (2)

A 54-year-old doctor presented with a 1-year history of early morning stiffness of her hands and Raynaud's. She had self-medicated with a number of NSAIDs which had helped to ease the pain and stiffness. She was seen by a rheumatologist who found a slight deformity of her fingers but no other signs of rheumatoid arthritis. In view of the long history, she was prescribed sulphasalazine as a disease-modifying drug. A month later she developed a severe, itchy, morbilliform rash all over her body. This settled on stopping the sulphasalazine, which contains a sulphonamide and 5-ASA.

- **Progress.** Both cases resolved on stopping the drugs.

Remember

Always discuss the harm/benefit ratio of drugs with your patient. Also review their current drug therapy and check for interactions.

Classification

- Type A: augmented (~80% of all ADRs) – exaggerated responses to known effects of the drug. Predictable and dose-related, e.g. skin necrosis after extravasation of vincristine, alopecia due to cytotoxic agents, cheilitis due to retinoids, urticaria triggered by opiates causing mast cell degranulation.
- Type B: unpredictable/bizarre – idiosyncratic and therefore more difficult to diagnose (see below).

Physiology

There are a number of mechanisms but the pathogenesis of many cutaneous ADRs remains unknown.

Cutaneous ADRs can also be categorised morphologically into three groups:

1. Skin reactions specific to drugs
2. Rashes potentially caused by drugs
3. Established skin disease exacerbated by drugs.

Skin reactions specific to drugs

Fixed drug eruptions are very rare. They develop within 24 h of drug ingestion and are usually localised areas showing sharply demarcated, round, red, oedematous (and sometimes bullous) plaques that become violaceous or hyperpigmented with time. Lesions recur at the same site on re-exposure to the drug.

Pigmentation caused by drugs

- Long-term amiodarone or chlorpromazine: purple/slate-grey pigmentation on sun-exposed sites
- Long-term minocycline: blue/black pigmentation of skin, nails, buccal mucosa, scars (may be irreversible)
- Mepacrine: reversible yellow skin pigmentation
- Bleomycin: flagellate erythema then hyperpigmentation of trunk.

Rashes potentially caused by drugs

There are many different reaction patterns and only a few common ones will be considered here:

Maculopapular/exanthematic eruptions

This is the most common type of cutaneous ADR. It is thought to be a cell-mediated reaction (may also be immune complex) involving CD8 T cells (Table 17.1). There are widespread, symmetrical, itchy eruptions. Macules and papules may become confluent and develop into a sheet-like erythema, sometimes with fever and eosinophilia. When due to a drug, it usually begins on the trunk. Suspect a viral aetiology if it starts on the face and moves down and if there is associated lymphadenopathy and conjunctivitis. After withdrawal of the drug, it usually settles over 2 weeks.

Note: if this eruption has progressed rapidly over 24 h it may herald the onset of the following:

- **Erythroderma.** In which > 90% of the skin surface is erythematous and inflamed. 10% of cases are drug induced (e.g. sulphonamides, sulphonylureas, penicillins, barbiturates, allopurinol, gold, mercury, arsenicals).
- **Toxic epidermal necrolysis (TEN).** The development of vesicles and/or bullae and skin tenderness raises this possibility (this might

Table 17.1 Pathogenesis of some cutaneous ADRs (hypersensitivity reactions)

Type	Examples
Type 1	
Immediate, IgE-mediated hypersensitivity	Urticaria and anaphylaxis due to penicillins
Type II	
Cytotoxic	Allergic thrombocytopenic purpura
Type III	
Immune complex formation	Morbilliform maculopapular rash Serum sickness Vasculitis, e.g. allopurinol and penicillin
Type IV	
Cell mediated	Allergic contact dermatitis to topical medicaments Erythema multiforme, toxic epidermal necrolysis Lichenoid drug eruption

then be followed by 'sheeting off' of the epidermis, see below). Mucosal involvement also suggests TEN.

- **Anti-convulsant hypersensitivity syndrome.** This is not just a severe ADR from an anti-convulsant but a distinct syndrome that, if undiagnosed, can lead to the death of patients if they are changed over to a different anti-convulsant that cross-reacts. The rash normally starts 2–4 weeks after starting any of the aromatic anti-convulsants (carbamazepine, phenytoin, phenobarbital, primidone). The rash is a non-specific maculopapular eruption that may involve mucosal surfaces and occasionally pustulates. The distinguishing clinical features from a 'normal' ADR are any of the following features:

- Fever
- Hepatosplenomegaly/lymphadenopathy
- Conjunctivitis/peri-orbital oedema
- Arthralgia
- Pharyngitis
- Severe malaise.

Blood tests may show:

- Eosinophilia
- Lymphocytosis with atypical lymphocytes
- Raised hepatic transferases.

If the drug is not stopped immediately the patient may progress to multi-organ failure and need ITU care. *All* aromatic anti-convulsant drugs must be avoided in the future because further exposure is likely to lead to an even more severe reaction. Sodium valproate is a reasonable alternative.

- **Photosensitivity** (see Table 17.2). Reactions range from erythema to blistering and characteristically spare the submental area, finger webs, under-eyebrow area and triangle of skin behind the ear lobe.

- **Lichenoid eruption** (see Table 17.2). Similar to idiopathic lichen planus but often more widespread and rarely involves mucous membranes.

The spectrum of erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

The classification of these diseases is confusing in the literature.

- **Erythema multiforme (EM)** 10% of cases are drug related (the majority are post-infectious, e.g. HSV, mycoplasma). They are mild and self-limiting, and usually resolve within 2–4 weeks. They are characterised by target lesions of a central dusky erythema (sometimes with blistering), a pale oedematous ring and a peripheral erythematous ring. These usually occur acraly (extremities) and symmetrically on extensor surfaces. They involve palms and soles. Mucosal involvement may be present but is mild and limited to one mucosal surface, e.g. the oral cavity.
- **Stevens–Johnson syndrome (SJS) (also called erythema multiforme major)** This is a more severe and extensive eruption. Widespread atypical target lesions appear on the trunk, in which epidermal necrosis results in the formation of blisters and epidermal detachment involving < 10% of body surface area. At least two mucosal surfaces are involved (oral, ocular, genital). Mucosal lesions are often more prominent than skin lesions. Systemic toxicity may occur. Usually resolves within 6 weeks.
- **Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap** When the extent of epidermal detachment is between 10% and 30% of the body surface area, in the presence of other features of SJS, this is considered an SJS/TEN overlap. The skin lesions are often necrotic blisters rather than target lesions and mucosal lesions are prominent and severe.
- **Toxic epidermal necrolysis (TEN)** This is of sudden onset (usually evolves over 24–48 h) with widespread morbilliform or confluent dusky erythema with skin tenderness, followed by widespread blistering (necrolysis) of the skin with histological evidence of full-thickness epidermal necrosis, subepidermal separation and a sparse or absent dermal infiltrate. Nickolsky sign is positive. Mucous membrane involvement is usually severe, including ocular, genital, oral, nasopharynx and GI tract; mortality 20–30%.

Adverse prognostic factors include:

- Age > 60 years
- Area of involved skin > 50%
- Plasma urea > 17 mmol/L
- Neutropenia < $1.0 \times 10^9/L$
- Idiopathic nature of TEN.

If extensive:

- Ventilation may be required
- Contact ITU, dermatology and ophthalmology urgently.

• Treatment of TEN

- Early high-dose immunosuppression may help but remains controversial (intravenous immunoglobulin is also commonly used).
- Analgesia (opiate).
- Dressings/human skin bank/autologous skin grafts.
- Eye protection and review for scarring.

- Pressure-relieving bed.
- ITU-supportive therapy.

Remember

- All cases of TEN should be considered to be drug-induced and suspected drug(s) should be stopped immediately
- The most common drugs responsible are sulphonamides, penicillins, anti-convulsants and NSAIDs.

Established skin disease exacerbated by drugs (Table 17.2)

- Psoriasis: can be destabilised by lithium and possibly beta blockers and anti-malarials.
- Acne: can be aggravated by progesterone-containing contraceptives, lithium and corticosteroids.
- Rosacea: worse with topical steroids.
- Peri-oral dermatitis (POD): caused and exacerbated by topical steroids.

Diagnosis of adverse drug reactions

The key elements to a diagnosis are a meticulous drug history and a high index of suspicion.

- Exclude other causes by history and examination.
- Take a careful drug history: remember to ask about over-the-counter preparations, e.g. laxatives, tonics and cough medicines, vitamins and complementary treatments.
- Start and stop dates of medication and relationship to onset of the rash.
- When the eruption begins from 7 to 21 days after the first administration of a drug or within 48 h if the drug has caused a similar reaction in the past, this is highly suggestive of an ADR.
- The timing is incompatible with an ADR if the drug was started after the onset of cutaneous or mucous membrane signs. If the onset is within 24 h of the first dose, or more than 21 days after stopping the drug, a drug aetiology is doubtful. If there are several drugs, each should be considered as a potential cause.
- Consult drug information for previous reports.

Table 17.2 Common drug associations

Maculopapular eruption	Photosensitivity	Lichenoid eruption
Antibiotics (Penicillins, sulphonamides)	Thiazides Sulphonamides	Gold Beta blockers
Anticonvulsants (Carbamazepine, phenytoin)	Amiodarone Tetracycline	Quinine/ anti-malarials Thiazides
NSAIDs	Nalidixic acid	Allopurinol

Investigations

These are of little help!

- Blood eosinophilia (may be found in toxic erythema but is non-specific)
- Biopsy 'may suggest but not prove a drug aetiology':
 - Lots of eosinophils: common
 - Lichenoid pattern: rare
 - SLE pattern: rare
 - Vasculitis: sometimes
- Blood level of drug (may be useful to check for over-dosage)
- If a fixed drug eruption is suspected re-challenge may be helpful (in other situations it is rarely justifiable for fear of precipitating a more severe reaction)
- Patch testing is helpful in patients with suspected allergic contact dermatitis (type IV hypersensitivity reactions) but *cannot* be used for systemic adverse drug reactions

Treatment

- Withdraw drug(s): symptomatic treatment with oral anti-histamines, topical steroids and moisturizers.
- Severe reactions (SJS and TEN) require supportive therapy and monitoring of infection, fluid balance and temperature. Patients may need ITU. Use of systemic immunosuppression may be considered if patients are seen within the first 24 h of onset.
- Dressings: leave on.
- Support mattress.
- Opiate analgesia.
- Give written information to patient and doctors to ensure no repeat exposure.

Figure 17.5 can be used as a guide to referral.

Further reading

Eshki M, Allamore L, Musette P et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2009; **145**: 67–72.

HIV AND THE SKIN

- Up to 90% of HIV-positive patients will develop a mucocutaneous disease, sometimes related to drug therapy.
- 30–40% of people with AIDS will suffer from three different dermatoses.
- A rash may be the presenting sign of HIV infection or AIDS (remember that up to 30% receive their diagnosis of AIDS and HIV at the same time, suggesting a large pool of undiagnosed patients).
 - **Cases:** Two patients with HIV presented to the clinic with different rashes, both of which are commoner in HIV patients. One presented with an eosinophilic folliculitis and the other with Stevens-Johnson/toxic epidermal necrolysis (see Fig. 17.6a and b).
 - **Progress:** Both patients were referred to the HIV specialist for HAART.

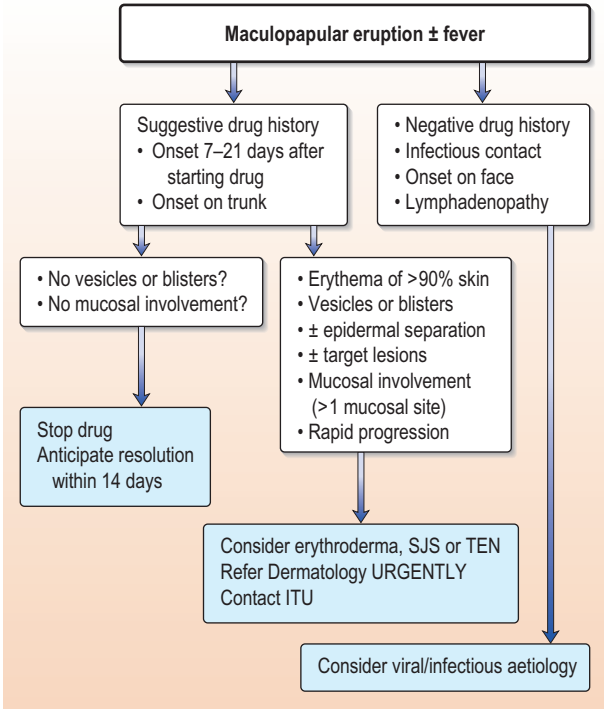


Figure 17.5 When to refer to a dermatologist in the case of an adverse drug reaction. SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

What dermatoses have commonly been the presenting illness of HIV (or indeed other causes of immunosuppression)?

- Extensive molluscum contagiosum in an adult
- Kaposi's sarcoma
- Extensive seborrhoeic dermatitis or eosinophilic folliculitis
- Pruritic papular eruption (PPE; also called itchy folliculitis) of HIV
- Extensive oro-pharyngeal candida
- Hairy leucoplakia.

Why is the skin so frequently affected?

The exact mechanisms are not known but include:

- Immune deficiency: increased infection
- Poor immune surveillance: increased skin tumours
- Post infective: reactive arthritis
- Autoantibodies: Sjögren's syndrome, polymyositis, ITP, pemphigoid, vitiligo, alopecia areata



Figure 17.6 Rashes associated with HIV. a) Eosinophilic folliculitis – a classical HIV dermatosis (courtesy of Dr Michael Ardern Jones). b) Stevens-Johnson/toxic epidermal necrolysis is more common in HIV (courtesy of Dr David Paige).

- Aberrant immune function TH1 to TH2 switch: eczema, pruritus, PPE
- Graft-versus-host disease (GVHD): lichen planus, erythroderma.

What type of rashes are seen?

Many different rashes are seen, which can be arbitrarily divided:

- Cutaneous infection
- Opportunistic infection
- Malignancy (BCC, SCC, KS, malignant melanoma)
- Papulo-squamous/inflammatory
- Oral lesions.

HAART has reduced the incidence of all skin lesions.

How would you diagnose the rashes?

The diagnosis can be difficult as frequently the rash is very extensive or there is an atypical clinical presentation. One should always have a low index for doing:

- Skin biopsies: both for all the routine stains and for culture of bacteria, fungi, viruses and AFBs.
- Skin swabs.
- Serology screens.
- Investigation of other 'organs' such as blood, stools, sputum, bone marrow: furthermore, treatment is often problematic as HIV rashes (even those that are common in immunocompetent people) tend to be

resistant to standard therapies and the use of immunosuppressive drugs is usually contraindicated.

Information

Cutaneous infections in HIV

- Bacterial: impetigo (*Staphylococcus aureus*), cellulitis/erysipelas (streptococci). Clinically, these infections tend to look much the same as in immunocompetent individuals. Deep-seated ecthyma may be seen.
- Viral:
 - Herpes: may present with blisters, often extensive and ulcerative, especially perianally and orally
 - Shingles/VZV: often painful, verrucous and extending over more than one dermatome and may be bilateral
- Fungal: dermatophyte and candidal infections are common in the skin and present typically. They often require systemic anti-fungal therapy for eradication (e.g. itraconazole 100 mg × 2 daily for 2–4 weeks)

What opportunistic infections occur in the immunocompromised and how would you distinguish between them?

Information

Failure to diagnose scabies (especially crusted scabies) can lead to a high proportion of medical staff becoming infected.

A variety of normally non-pathogenic organisms have been described in AIDS and other immunosuppressed patients. Clinically they are difficult to distinguish:

- Cutaneous CMV may present with blisters, ulcers or necrotic lesion.
- Fungi are common culprits and may present with nodules (often deep subcutaneous) or scaly papules (*Cryptococcus* is seen in the UK whereas *Histoplasma* is more common in the US).
- Scabies presents typically with itchy papules and burrows in the web spaces, the wrists, genitalia, palms/soles. Crusted scabies ('Norwegian scabies') presents atypically with a rather crusted eczematous-looking rash often centred around the web spaces and it may not be itchy.
- Non-tuberculous or 'atypical' mycobacteria are a particular problem in advanced AIDS and present with papules, nodules, ulcers or sporotrichosis-like lesions.

These infections can be localised to the skin but also present as a systemic infection. Malaise, fever, abdominal pain, headache or diarrhoea may be non-specifically suggestive of systemic infection. Biopsy and culture is the best way to diagnose these rashes.

What is hairy leucoplakia due to and what does it look like?

It is due to the Epstein-Barr virus in an immunosuppressed patient and is almost unique to HIV patients. It is a relatively late sign of HIV disease.

Clinically, white plaques appear on the sides of the tongue. Vertical ridging or corrugations are seen within the plaques. Unlike candidal infections, there are no small satellite lesions around the edge and the white material cannot be scraped off to leave raw areas underneath.

What types of malignancy occur in immunocompromised patients?

- The two most common types of skin cancers (BCC and SCC) appear to be increased in HIV-positive patients. They look the same as in immunocompetent patients.
- Malignant melanoma may be increased in prevalence. The clinical appearance is typical.
- Kaposi's sarcoma is more common and more severe in AIDS patients (without available HAART therapy) than in classical KS or African KS. It presents as purplish-brown plaques and nodules. The nose, palate and genitalia seem common sites but remember they can spread internally. KS is predominantly seen in men who have sex with men with AIDS and, for unexplained reasons, the incidence declined during the 1990s but has been increasing again since 2000. There is a strong link between herpes virus type 8 and the development of all types of KS, although other factors might be involved, as not all people with HHV type 8 get KS.
- Lymphomas are more common with HIV and may present with lymphadenopathy, pleural effusions, night sweats and weight loss.

What are the more common 'papulo-squamous' dermatoses encountered in HIV patients?

The 'papulo-squamous' dermatoses encountered are:

- Seborrhoeic dermatitis: 80%
- Unexplained pruritus: 40%
- Xerosis, ichthyosis: 30%
- Pruritic papular eruption (PPE): 20%
- Eczema: 10%
- Psoriasis: 5%
- Drug rashes: 20%.

In general, these rashes become more common (and severe) with progression of the disease.

Seborrhoeic dermatitis

Itchy, red and scaly eczematous rash in the seborrhoeic areas (sides of nose, around eyes, forehead, scalp, sternum, glans penis). This looks similar to seborrhoeic dermatitis in immunocompetent patients but is often more extensive. It may appear in early 'asymptomatic' HIV disease.

- **Therapy:** Topical miconazole/hydrocortisone cream, emollients, ketoconazole shampoo. If resistant, consider topical 0.1% tacrolimus ointment, topical lithium and oral itraconazole 100 mg × 2 daily for 2 weeks.

Pruritus and xerosis (dry skin)

These often go together and the aetiology is unclear. Again they may be early manifestations of advanced HIV disease.

- **Therapy:** Emollients, bath oils, aqueous cream as soap substitute. Sedating anti-histamines (e.g. hydroxyzine or chlorphenamine).

Consider 0.5% menthol in aqueous cream or crotamiton. Phototherapy if resistant.

PPE (pruritic papular eruption; also called itchy folliculitis)

A unique papular and (at times) pustular eruption centred on hair follicles. This is intensely itchy and usually involves the upper trunk, back and the proximal arms. Papules tend to arise, grow in size, frequently have the top scratched off and then recede as other new lesions arise. In African-Caribbean patients lesions are often larger and more frequently involve the face. Skin biopsy reveals a lymphohistiocytic infiltrate around blood vessels and hair follicles, often accompanied by eosinophils.

The so-called unique HIV rash 'eosinophilic folliculitis' is probably a variant of PPE.

PPE tends to appear in more advanced HIV disease and becomes worse as CD4 counts fall.

- **Therapy:** Medium-strength topical steroids, oral anti-histamines and low-dose long-term antibiotics (as used in acne) may help. Isotretinoin (20–40 mg daily) or PUVA is effective for resistant cases.

Eczema

The prevalence of eczema is probably increased in HIV patients, reflecting the eosinophilia and high IgE levels that are commonly seen. It looks similar to eczema in immunocompetent patients.

- **Therapy:** As for normal eczema.

Psoriasis

The prevalence of psoriasis is increased in HIV (5% versus 2% in the normal population); 30% may get psoriatic arthropathy (versus 5% of normal psoriatics). The disease can be typical with red, scaly plaques on elbows and knees, and scaling in the scalp. However, psoriasis occasionally becomes severe and widespread in advanced HIV patients. They may become erythrodermic or develop pustular psoriasis, especially on the soles of the feet. When the latter happens there is clearly an overlap with reactive arthritis.

- **Therapy:** Topical steroids, calcipotriol (a synthetic vitamin D₃ analogue) and tar compounds will help mild cases. UVB or PUVA is useful for more advanced disease. Although there is some in vitro evidence that phototherapy may promote HIV replication, this has not been shown to be a problem in clinical practice.

Oral drugs for severe disease include acitretin or anti-retroviral drugs.

The other drugs used in 'normal' psoriasis include methotrexate, ciclosporin and hydroxyurea. Biological agents are now being used.

Further reading

Rodgers S, Leslie KS. Skin infections in HIV-infected individuals in the era of HAART. *Current Opinion in Inf Dis* 2011; **24**: 124–129.

NB: Page numbers in *italics* refer to boxes, figures and tables.

A

- Abbreviated Mental Test (AMT),
154, 154, 156, 161
- ABCD² score (stroke risk), *175*
- ABCDE basic life support,
280–283, 281
- Abdominal pain, *43–50*
 case history, *43*
 differential diagnosis, *44*
 investigations, *43–45*
 management, *44*
 patient information, *44–45*
- Abiotrophia* spp, *310*
- Abscesses
 liver *see* Liver abscess
 lung *see* Lung abscess
 pyogenic, *358*
 subphrenic *see* Subphrenic
 abscess
- Absorption, reducing, *397*
- Acamprosate, *72*
- Accelerated hypertension, *320*
- Acebutolol, *301*
- Acetaminophen *see* Paracetamol
- Acetazolamide, *465*
- Acetylcholine esterase inhibitors,
158
- Acetylcysteine, *397, 401–403*
- Aciclovir, *17, 17, 483*
- Acidosis, *241–243*
 case history, *241–242, 242*
 HCO₃, role, *243, 244*
 management, *417*
 underlying problems, *242–243*
- Acinetobacter* spp, *350*
- Acitretin, *564*
- Acquired bleeding disorders,
106
- Actinobacillus*
actinomycetemcomitans, *310*
- Acute abdominal pain, *56*
- Acute Addison's disease, *443*
- Acute alcohol withdrawal, *34*
- Acute anxiety, *532–534*
 associated conditions, *533*
 case history, *532*
 management, *532–533*
 signs/symptoms, *533*
- Acute arrhythmias, treatment,
273–274, 273
- Acute asthma *see* Severe acute
 asthma
- Acute autoimmune rheumatic
 disease, *202–206*
- Acute back pain, *213–215*
 case history, *213*
 examination, *214–215*
 investigations/diagnosis/
 management, *214–215, 214*
- Acute breathlessness *see*
 Breathlessness, acute
- Acute chest syndrome, *89*
 treatment, *89*
- Acute cholecystitis, *74, 75*
- Acute colitis, *40, 40, 41*
- Acute coronary syndromes,
284–286, 336
 classification, *288*
 symptoms, *288*
- Acute cough, *327–328*
- Acute diarrhoea, *37*
- Acute disseminated
 encephalomyelitis (ADEM)
 case history, *484*
 diagnosis, *484–485*
- Acute dystonic reactions, *504–505*
- Acute glomerulonephritis (GN),
251–253
 case history, *251*
 rapidly progressive, *253*
- Acute haemolysis, *102, 105*
- Acute heart failure (AHF),
233–238, 297–298
 case history, *233, 297*
 management, *236–238, 294*
 treatment, *297–298*

- Acute hot joint, 182–183
 case history, 182
 causes, 182
 examination, 183
 history taking, 182
 investigations, 183
 management, 183
- Acute kidney failure, 234
 RIFLE classification, 234
- Acute kidney injury, 245–246
 case history, 245
 dialysis, indications, 246
 investigations, 245–246
 priorities, 245–246
 renal unit referral, 246
- Acute leukaemias, 97–98, 134
 features, 138
- Acute limb ischaemia, case
 history, 324
- Acute liver disease, 63
 investigations, 63, 63
- Acute lung injury (ALI), 390–393
 case history, 390
 causes, 391
 features, 391, 391
 investigations, 390
 management, 390–392
 pathophysiology, 391–392
- Acute lymphoblastic leukaemia
 (ALL), 139
- Acute myeloid leukaemia (AML),
 134, 134, 139
 investigations, 134
- Acute myocardial infarction (MI),
 172–173, 173, 288–289
- Acute myocardial ischaemia,
 291–292
- Acute pancreatitis, 44, 45
- Acute pulmonary oedema, 172,
 173
- Acute respiratory distress
 syndrome (ARDS), 390–392,
 391
- Acute respiratory failure, 341
- Acute urticaria, 546
- Addison's disease, 442–444
 case history, 442
 clinical findings, 443
 investigations, 444
 management, 443–444
 treatment, 446
- Adenocarcinoma, 46
- Adenosine, 271, 274
- Adrenal failure, causes, 443
- Adrenal insufficiency, 442
- Adrenaline (epinephrine), 547
- Adrenocorticotrophic hormone
 (ACTH) test, 444
- Adverse drug reactions (ADR) *see*
 Cutaneous adverse drug
 reactions (ADR)
- β_2 agonists
 long acting (LABA), 332
 short acting (SAB), 330–332
- Agranulocytosis, 436
- AIDS *see* HIV/AIDS
- Akinetic-rigid syndromes, 504
- Albumin, 258
- Alcohol
 acute withdrawal, 34
 deliberate self-harm (DSH),
 531–532
 delirium tremens (DT), 520
 side effects, 515
see also Excess alcohol use
- Alemtuzumab, 482
- Alendronate, 217
- Alfacalcidol, 452
- Allopurinol, 183, 256
- Alzheimer's disease (AD), 519
 management, 158, 158
- American Psychiatric Association,
 153
- Amiloride, 187, 187
- Aminophylline, 330, 331, 348
- Amiodarone, 187, 433, 439–444
 heart conditions, 274–277, 300
- Amitriptyline, 17, 377, 514
- Amourosis fugax, 466
- Amoxicillin, 7, 19, 162–163,
 186–187, 494
 adverse reactions, 553–554, 554
 pneumonia, 353, 360
 respiratory conditions, 343, 345,
 348, 361–362
- Amphetamine, 515
- Amphotericin, 378
- Ampicillin, 19
- Amyloid, treatment, 258
- Anaemia, 77–81
 assessment, 77
 cancer, 142–144
 causes, 140
 chronic kidney disease (CKD),
 141, 250
 classification, 77, 78

- defined, 77–80
- drug-induced, 140
- haemolytic *see* Haemolytic anaemia
- investigations, 77
- iron deficiency *see* Iron deficiency anaemia
- leucoerythroblastic, 143–144
- liver disease, 141–142
- macrocytic *see* Macrocytic anaemia
- microcytic *see* Microcytic anaemia
- pernicious (PA), 83, 140
- rheumatoid arthritis (RA), 140–141
- Anaesthetic agents, 515
- Anagrelide, 100
- Anaphylactic shock, 408–409, 408
 - examination, 408
 - history taking, 408
 - management, 408–409
 - prevention, 409
- ANBP2 trial, 321
- Androgens, 84
- Aneurysm, 461, 463
 - features, 284–285
 - investigations, 285–286
- Angina, 336
- Angio-oedema, 545–546
 - hereditary (HAE), 547–548, 548
 - investigations, 548
 - management, 547–548
- Angioplasty, 387
- Angiotensin-converting-enzyme (ACE), 322
- Angiotensin-converting-enzyme (ACE) inhibitors, 236–237
 - cough, 327
 - heart conditions, 173, 297–298, 301–302, 304–305
 - hypertension, 321
 - side effects, 321
- Angiotensin-receptor antagonists, 304–305, 327
- Anti-arrhythmics, 513
- Antibiotics, 13, 60, 132, 162–163, 364, 494
 - neutropenia, 377–378
 - pneumonia, 353–354, 356
 - side effects, 514
- Anti-coagulant drugs, 171, 302, 309
 - heart disease, 172–173
 - orally active, 119
 - overdosage, 111–112
 - see also* Heparin; Warfarin
- Anti-convulsant hypersensitivity syndrome, 556
- Anti-convulsants, 514
- Anti-depressants, 514
- Anti-dopaminergics, 505–506
- Anti-emetics, 514
- Antiglobulin (Coombs') tests, 101, 128
- Anti-histamines, 514, 547
 - H₁, 546
 - H₂, 546
- Anti-hypertensive drugs, 321–323
- Anti-infective drugs, 514
- Anti-inflammatory drugs, 515
- Anti-malarials, 514
- Anti-muscarinic drugs, side effects, 514
 - signs, 514
 - treatment, 514
- Anti-neutrophil cytoplasmic antibody (ANCA) points, 252, 253
- Anti-phospholipid syndrome, 208, 208
 - management, 209
- Anti-platelet agents, 171, 301
- Anti-psychotics, 511, 512, 514
- Anti-retroviral drugs, 564
- Anti-spasmodics, 514
- Anti-TNF α agents, 199
- Anuria, 230
- Anxiety
 - syncope, 266
 - see also* Acute anxiety
- Aortic dissection, 291, 336
- Aortic regurgitation (AR), 307–308
- Aortic sclerosis, case history, 306
- Aortic stenosis (AS), 306–308, 307
 - vs hypertrophic cardiomyopathy (HCM), 317, 318
- Apomorphine, 185
- Apraxic gait, 499
- Arrhythmias, 150
 - acute, 273–274, 273
 - early ventricular, 299
 - late, 300
 - poisoning, 396–397

- Arrhythmias, post-infarction, 298–300
 case history, 298–299, 299
- Arterial blood gas (ABG)
 sampling, 339, 339, 341, 341, 343–344, 387
- Arterial disease, 542
 ulcers, 543
- Arteriosclerotic parkinsonism, 184
- Arteritis, 181–183
 assessment, 181–182
 case history, 181
 hospital discharge, 181–182
- Artesunate, 16
- Arthralgia, 379
- Arthritis, 106
- Ascites, 64–66
 case history, 64–65
 investigations, 64–65, 64–65
- Asparaginase (crisantapase), 515
- Aspergilloma, lung disease, 334
- Aspergillus* spp, pneumonia, 355
- Aspergillus fumigatus*, 23
- Aspiration, 170
 knee, 219
- Aspirin, 19, 100, 213, 467, 544
 haemolysis, 102, 102
 heart conditions, 172, 285, 289, 297, 301
 stroke, 169, 171, 474
 transient ischaemic attack (TIA), 175, 476
see also Salicylate overdose
- Assessment scales, 163
- Asthma, 328–332
 acute *see* Severe acute asthma
 causes/triggers, 329
 differential diagnosis, 328
- Atenolol, 301, 513
- Atheromatous renovascular disease, 238
- Atonic seizures, 498
- Atorvastatin, 302, 474
- Atrial fibrillation (AF), 270, 274–277, 300, 348
 cardioversion, 273, 276
 case history, 275
 heart failure, 439
 management, 275, 277
 prevalence/risks, 274
 thromboembolism, 276
- Atrial flutter, 270
- Atrial tachycardia, 270
- Atropine, 300, 407, 514
- Atypical meningitis, 494
- Autoimmune haemolytic anaemia (AIHA)
 diagnosis, 85
 management, 85–86
- Autoimmune rheumatic disease, acute, 202–206
- Automatic implantable cardioverter defibrillator (AICD), 283, 283
- AV nodal re-entry tachycardia (AVNRT), 270
- Avascular necrosis, femoral head, 90
- Axonal injury, 489
 case history, 489
- Azathioprine, 86, 202, 213
- B**
- B₁₂ deficiency, 81, 82
 causes, 82
- Back pain
 acute *see* Acute back pain
 severe, 215–217
- Bacteraemia, defined, 4
- Bacterial chest infection, 23
- Bacterial meningitis, 493
 treatment, 494
- Bacterial sepsis, 144–145
- Balloon tamponade, 69
- Barbiturates, 514–515
- Barrett's oesophagus, 46
- Barthel Index, 163, 164
- Bartonella* spp, 310
- Basic life support (ABCDE), 280–283, 281
- Bell's palsy, 468–469, 468
 investigations, 469
- Bence Jones protein, 216
- Bendroflumethiazide, 162–163, 323
- Benign paroxysmal positional vertigo (BPPV), 471
 case history, 471
 diagnosis, 471
 management, 471–472
- Benzodiazepines, 398, 535
 excess alcohol use, 35, 72
 side effects, 514–515
- Benzylpenicillin, 7, 17, 19, 542
 meningitis, 491, 494

- Beta-blockers, 433, 438
 heart conditions, 274, 277,
 285, 289–290, 295, 297–301,
 305
 side effects, 321, 513
- Beta-interferon, 481
- Bezold–Jatishch reflex, 268
- Bilateral subdural haematomas,
 477–478, 480
- Biochemical screening, 136
- Bismuth chelate, 515
- Bisphosphonates, 144, 213,
 216–217
- Bisoprolol, 298
- Blackouts, 149–151
 cardiovascular causes, 150
 case history, 149
 history taking, 149–150
 investigations, 150
 treatment, 150
- Bladder function, 170
- Bleeding disorders, 105–109
 acquired, 106
 case history, 105, 108–109
 inherited, 105–106, 106–107
 investigations, 106–109
 rectal *see* Rectal bleeding
see also Haematemesis/
 melaena
- Blood, colour, 333–336
- Blood pressure, 396
- Blood transfusion, 125–131
 case history, 126–127, 129
 complications, 129, 129
 investigations, 127–129, 128
- BODE index, 347, 347
- Bone marrow pathology, 99, 99
- Bone pain, 376
- Bornholm's disease, 337
- Bowel ischaemia, 243
- Bradycardia, 277–312
 case history, 278–279, 280
 diagnosis, 278
- Brain
 brain death, 492
 drugs affecting, 514
 neurological deficits, 168
 sodium concentration, 230
 trauma *see* Severe brain injury;
 Traumatic brain injury
see also entries beginning
 Cerebral
- Brainstem, stroke, 167–169
- Breathlessness, acute, 325–326
 assessment, 325–326
 case history, 325
 causes, 346
- Breathlessness/wheeze, 328–332
see also entries beginning
 Respiratory
- British National Formulary, 401
- British Thoracic Society, 285
- Bromocriptine, 514
- Bronchiectasis, 334
- Bronchodilators, 343, 345, 348
- Bronchus, carcinoma of, 333–334,
 372–378
 case history, 372
 complications, 377
 diagnosis, 372–378
 differential diagnosis, 374–376
 investigations, 373, 374–375, 379
 management, 376
 treatment, 376–377
- Brucella* spp, 310
- Busulfan, 100
- C**
- Cabergoline, 456
- Calcipotriol, 564
- Calcium, 213
- Calcium channel blockers, 301,
 321, 513
- Calcium gluconate, 452
- Calcium pyrophosphate, 209, 211
- Campylobacter* spp, 13, 225
- Candida albicans*, 355
- Cannabis, 515
- CAPRICORN trial, 298
- Captopril, 301–302
- Capture beats, 272
- Carbamazepine, 377, 456, 522, 556
- Carbapenem, 6
- Carbimazole, 187, 433, 435
- Carbon monoxide, 515
- Carboplatin, 376–377
- Cardiac arrest, 280–283
 basic life support (ABCDE),
 280–281, 281
- Cardiac conditions
 drugs, 513–516
 markers, chest pain, 287, 288
 pain, 336–338
 sarcoidosis, 379
 syncope, 265–266
- Cardiobacterium hominis*, 310

- Cardiogenic hypotension, 387
- Cardiogenic shock, 231, 292–293, 368
 case history, 292, 383
 causes, 384
 defined, 292
 management, 293, 294
- Cardiomyopathies, 315–317
 case history, 315–316
- Cardiopulmonary resuscitation (CPR), 188
 principles, 188–189
- Cardiovascular causes, blackouts, 150
- Cardiovascular support,
 poisoning, 396
- Cardioversion, 273, 276
- Carotid endarterectomy, 172, 175
- Carotid sinus, 265
- Carvedilol, 298, 513
- Catecholamine crisis *see*
 Pheochromocytoma
- Catechol-O-methyl transferase (COMT) inhibitors, 185
- Cawthorne–Cooksey exercises, 471–472
- Cefaclor, 364
- Cefotaxime, 6–7, 494
- Ceftazidime, 6, 356, 377
- Ceftriaxone, 6–7, 9
- Cefuroxime, 14, 132, 261, 358, 364, 392–393
 septicaemia, 6–7
- Cellulitis, 541
 treatment, 542
- Central nutrition, 29
- Central vestibular lesion, 470
- Cephalosporin, 5–6, 40
- Cerebral granulomatous angiitis
 case history, 476
 investigations, 476–477
- Cerebral haemorrhage, 472
- Cerebral infarction, 472–474, 473, 478
- Cervical myelopathy, 500
- Chemotherapeutic drugs, 515
- Chest conditions
 HIV/AIDS, 22–24
 ‘silent’, 331
see also Acute chest syndrome
- Chest pain, 284–286, 336–338
 assessment, 284
 cardiac markers, 287, 288
 case history, 284–285
 causes, 284
 differential diagnosis, 336–338
 investigations, 338
- Chlamydia psittaci*, 350
- Chlamydia spp*, 310
- Chloramphenicol, 494
- Chlordiazepoxide, 522
- Chlormethiazole, 522
- Chloroquine, 16, 514
- Chlorphenamine, 547, 563–564
- Chlorpromazine, 514
- Chlorpropamide, 456
- Cholangitis, 60
- Cholecystitis, 73–75
 case history, 73
 diagnosis, 75
 investigations, 73, 73, 74
- Chondrocalcinosis of knee, 210
 investigations, 210
 management, 210–211, 210
- Chronic Addison’s disease, 443
- Chronic cough, 327
- Chronic haemolytic anaemia, 147
- Chronic kidney disease (CKD), 109, 223–227
 anaemia, 141
 case history, 247
 features, 248
 investigations, 247–250, 247
 management, 249
 multidisciplinary approach, 249
 patient preparation, 249–250, 250
 specific conditions, 250
 stages, 247–248
- Chronic liver disease, 65
 management, 65–66
- Chronic lymphoblastic (lymphocytic) leukaemia (CLL), 83–84, 85, 132, 139
 features, 132, 133
 management, 132–133
 treatment, 133
- Chronic myeloid leukaemia (CML)
 diagnosis, 137
 investigations, 137
 referral, 137
- Chronic obstructive pulmonary disease (COPD), 328, 341, 344–349
 case history, 345, 347

- examination, 345
 key points, 345–347
 prognosis, 346–347
 Chronic pain, 337
 Chronic respiratory failure, 341
 Chronic urticaria, 546
 Chvostek's sign, 450
 Ciclosporin, 40, 256, 547
 Cimetidine, 515, 546
 Ciprofloxacin, 7, 14, 60, 102, 261, 353, 361–362, 377
 Cisplatin, 376
 Citalopram, 160
 Cladribine, 482
 Clarithromycin, 353
 Clock-drawing tests, 156, 157
 Clonazepam, 499
 Clopidogrel, 169, 171, 175
 heart conditions, 286, 289, 297, 301
Clostridium difficile, 6, 39, 186–187
 pseudomembranous colitis, 9–10, 10
 'Clouding of consciousness', 509, 516
 Cluster headache, 503
 case history, 503
 causes, 503
 Co-amifofruse, 187
 Co-amoxiclav, 353, 357
 Co-beneldopa, 479
 Cocaine, 404–407, 405
 case history, 405
 side effects, 515
 toxicity features, 406
 Co-careldopa, 478–479, 478
 Coeliac disease, 50, 51, 51
 Cognitive screening, 519
 Colchicine, 183, 256
 Colon cancer, 53–54
 case history, 53
 patient advice, 53–54, 54, 55
 risks, 54
 Colonoscopy, 53, 53
 Colorectal cancer, distribution, 55
 Coma, 492
 Community-acquired pneumonia (CAP), 350
 antibiotics, 353–354
 case history, 350, 352
 diagnosis, 351
 infecting organisms, 350
 investigations, 350, 352–353, 352
 severity, 350–351
 signs, 350–357
 Community-acquired
 Staphylococcus aureus, 310
 Community-acquired *Streptococcus pneumoniae*, 350
 Complete heart block, 278
 Compression bandages, 543
 Confusional Assessment Method (CAM), 153–154
 Constipation, 36–37
 case history, 36
 causes, 37
 treatment, 37
 urinary tract infection (UTI), 181
 Consultant in Communicable Disease Control (CCDC), 8, 13–14, 23
 Coombs' tests, 101, 128
 COPERNICUS trial, 298
 Cor pulmonale, 312–313, 348
 investigations, 314
 management, 313
 pathophysiology, 313
 prognosis, 313–314
 Corticosteroids, 19, 22, 85, 183, 362, 547
 asthma, 330–332
 side effects, 515
 Cortisol, 84, 430
 Co-trimoxazole, 21–22, 102
 Cough, 326–328
 associated features, 328
 case history, 327
 investigations, 328
 syncope, 265
Coxiella burnetii, 310
 Cranial (giant cell) arteritis, 212–213
 case history, 212
 differential diagnosis, 212–213
 features, 213
 investigations, 212
 steroids, 213
 Creatinine clearance, estimation, 247
 Crisantaspase (asparaginase), 515
 Crohn's disease, 40, 42
 vs ulcerative colitis, 40, 42
Cryptococcus spp fungal infections, 562
Cryptococcus neoformans, 23

- Crystal arthritis, 209–211
 case history, 209–210
- CURB criteria, community-acquired pneumonia (CAP), 351, 351
- Cushing's syndrome, 430–432
 case history, 431
 causes, 430
 diagnosis, 431–432
 management, 432
 signs/symptoms, 431
- Cutaneous adverse drug reactions (ADR), 553–559
 case history, 554
 classification, 555
 diagnosis, 558
 investigations, 559
 physiology, 555
 pigmentation, 555
 rashes, 555–558, 556
 skin disease, exacerbation, 558, 558
 skin reactions, 555
 treatment, 559, 560
- Cutaneous cytomegalovirus (CMV), 562
- Cyclizine, 88
- Cyclophosphamide, 202
- Cycloplegics, 514
- Cyclosporin, 564
- Cytomegalovirus (CMV), 23, 355, 562
- D**
- Dabigatran, 120, 368, 476
- Danazol, 548
- Dapsone, 22, 102, 102, 544, 547
- De Quervain's thyroiditis *see* Viral thyroiditis
- Deep vein thrombosis (DVT)
 diagnosis, 119
 investigations, 323, 368
 prophylaxis, 367
 treatment, 119–121, 323, 368
- Dehydration, 225, 415
- Deliberate self-harm (DSH), 527–532
 case history, 528
 management, 528–532
 treatment refusal, 530–531, 531
- Delirium, 153–156, 509–513
 Abbreviated Mental Test (AMT), 154, 154
 case history, 153, 509, 513
 causes, 155, 510
 Confusional Assessment Method (CAM), 153–154
 diagnosis, 153, 153, 509–513
 differential diagnosis, 512
 drug-induced, 513–532
 elderly, 153–156
 examination, 155
 features, 509
 history taking, 154
 investigations, 155, 510–511, 511
 management, 155–156, 511
 as mnemonic, 155
 nursing care, 511
 predisposing factors, 510
 prognosis, 512–513
 risk factors, 155
 treatment, 512, 514–515
- Delirium tremens (DT), 519–522
 case history, 520
 complications, 521
 features, 520
 investigations, 521
 long-term care, 522
 treatment, 521–522
- Delusions, persecutory, 510
- Demeclocycline, 459–460
- Dementia, 156–159, 516–519
 case history, 156, 517
 causes, 157, 517
 defined, 156–158
 differential diagnosis, 518
 examination, 518
 investigations, 157, 518–519
 management, 158, 519
 presentation, 517
- Dementia-like syndrome, 157, 157
- Depression, 159–161, 522–527
 assessment, 159–161, 160, 524–525, 524
 associated conditions, 522–523
 case history, 159, 523
 categorisation, 523
 causes, 532
 differential diagnosis, 524–525
 investigations, 524
 management, 160–161, 525–526
 treatment, 526–527
- Dermatology, 541–564
- Dermatoses
 HIV, 560, 561
 'papulo-squamous', 563–564

- Desmopressin, 456
- Diabetes insipidus (DI), 457–458
 case history, 458
 causes, 458, 458
 management, 458
- Diabetes mellitus, 411–429
 case history, 411, 413, 422–423
 diagnostic criteria, 411, 413
 hospital admission, indications, 411–413
 India, 428
 investigations, 423
 pregnancy *see* Pregnancy, diabetes mellitus
 spectrum, 412
 treatment, 423, 424
 type 1, 412, 413–414, 422–424, 426, 430
 type 2, 411, 412, 424–426
- Diabetes mellitus, surgery, 424–426
 assessment, 425
 case history, 424
 management, 425
 perioperative insulin, 426
 urgent, 426
- Diabetic foot, 427–429
 case history, 427
 classification, 428
 examination, 427–428
 history taking, 427
 management, 428–429
 pathogenesis, 428
- Diabetic ketoacidosis (DKA), 413–418
 assessment, 414, 417
 case history, 413–414
 causes of death, 417
 fluid replacement, 415–416, 416
 investigations, 414
 management, 415, 417
 presentation, 414, 415
- Diabetic nephropathy, treatment, 258
- Diagnostic and Statistical Manual (DSM), 4th edition (DSM-IV-TR), 153, 153
- Dialysis, 254–257
 avoiding, 254–257, 254, 255
 case history, 254
 indications, 246
 monitoring, 254–256
- Diamorphine, 87–88, 285, 297, 304
- Diarrhoea, 37–40
 case history, 38–39
 causes, 38–39
 diagnosis, 38–39
 differential diagnosis, 39–40, 42
 investigations, 37–40, 40
 management, 38
- Diastolic heart failure, 306
- Diazepam, 407, 499, 535
 acute anxiety, 532–533
 delirium tremens (DT), 522
- Diclofenac, 88, 121–122, 183, 187
 rheumatology, 196, 211, 214
- Diffuse axonal injury, 489
- Digoxin, 433, 513, 516
 heart conditions, 172, 274, 275, 277, 305
- Dihydrocodeine, 88
- Dihydropyridines, 301
- Dilated cardiomyopathy (DCM), 315
 management, 315–316
- Diloxanide furoate, 3
- Diltiazem, 321
- Dimercaprol, 102
- Diplopia, 461–465
 case history, 461, 463–464
 causes, 464
 investigations, 464–465
 treatment, 463–464
- Dipyradamole, 171, 474
- Disease-modifying anti-rheumatic drugs (DMARDs), 198–200
- Disodium pamidronate, 449
- Disseminated intravascular coagulation (DIC), 109–112
 case history, 110–111
 diagnosis, 110
 management, 111
- Disturbed patient, 537–540
 case history, 538
 causes, 537–538
 management, 538–540
 presentation, 537
- Diuretics, 321
- Do not attempt resuscitation (DNAR), 188–189, 189
- Dobutamine, 293, 295, 387
- Döhle bodies, 144
- Domperidone, 467, 505
- Donepezil, 158, 158, 519
- Dopamine, 293, 295

- Dopamine agonists (DA), 185, 456, 479
- Dopamine antagonists, 514
- Double vision *see* Diplopia
- Doxapram, 348
- Doxycillin, 353
- Doxycycline, 16
- Drop attacks, 486
- Drug reactions (ADR), adverse *see*
Cutaneous adverse drug
reactions (ADR)
- Drug users, pneumonia, 355
- Drug withdrawal, 515–516
- Drug-induced conditions
anaemia, 140
depression, 526
hyperkalaemia, 241
parkinsonism, 185
respiratory failure, 342
- Drug-induced illness, elderly,
186–189, 186
case history, 186–187
- Duke criteria, infective
endocarditis, 310
- Dyskinesia, 478–479, 479, 504
treatment, 479
- Dysphagia, 35–36, 170
case history, 35
diagnosis, 36
investigations, 35–36
- Dysuria, defined, 260–261
- E**
- Ecallantide, 548
- Ecstasy (methylenedioxymethamphetamine, MDMA) abuse, 405, 406–407
features, 406
investigations, 406
side effects, 515
treatment, 406–407
- Ectopic calcification, 255
- Eczema, 552, 564
management, 552
- Eikenella corrodens*, 310
- Electrolytes *see* Fluid balance/
electrolytes
- Electrophysiologist (EP), 277
- Elimination, active, 397
- Emboli, causes, 167
- Empyema, 365, 365
- Enalapril, 162–163, 327
- Encephalitis, 482–486
case history, 482
causes, 483
investigations, 483–484, 484
- Endocrine conditions, depression,
532
- Endoscopic retrograde
cholangiopancreatography
(ERCP), 59–61, 60
complications, 61
- Enoxaparin, 289–290, 357, 507
- Enoximone, 295
- Enteral feeding, 29, 29
- Enteric fever *see* Typhoid
- Enterococcus* spp, 6, 310
- Enterohaemorrhagic Escherichia coli*
(EHEC), 11–12
case history, 12
differential diagnosis, 12
investigations, 12
management, 13
- 'Eosinophilic folliculitis', 564
- Epilepsy, 498
alcohol dependence, 72
elderly, 149–150, 150
- Epinephrine, 547
- Epstein-Barr virus (EBV), 18–19,
63, 146–147, 562–563
case history, 18
diagnosis, 18
investigations, 18–19
treatment, 19
- Erythema multiforme (EM),
557
major *see* Stevens-Johnson
syndrome (SJS)
- Erythema nodosum (EN), 378–381,
543–548, 544
case history, 543
causes, 544
diagnosis, 543–545
referral, 545
treatment, 544–545
- Erythroderma, 550, 550, 555–557
- Erythromelalgia, toes, 96
- Erythromycin, 132, 353, 360–362
- Erythrovirus B₁₉*, 146, 147
- Escherichia coli* (*E.coli*), 4, 6–7,
11–13
- Escitalopram, 527
- Esmolol, 271
- Essential thrombocythaemia (ET),
99, 99–100

- Essential tremor, Parkinson's disease (PD), 184
- Etanercept, 141, 199
- Ethambutol, 22–23, 218, 362
- Ethanol, 397
- Etidronate, 217
- Etoposide, 376–377
- Exanthematic eruptions, 555–557, 556
- Excess alcohol use, 71–73
case history, 71
treatment, 71–73
- Extradural haemorrhage, 486
- Extrapyramidal side effects (EPSEs), 512
- F**
- Factor Leiden deficiency, 117
- Faecal occult bloods, 50
- Faints *see* Fits/faints; Syncope
- Falciparum malaria, features, 145–146
- Falls, elderly, 151–152, 485–486
case history, 151, 485–486
causes, 485
diagnosis, 485–486
examination, 151
investigations, 152
management, 152
questions, 151–152
- Famciclovir, 17
- Familial adenomatous polyposis, 53–54
- Familial hypocalcaemic hypercalcaemia (FHH), 448
- Favism, 103
- Febrile illness, causes, 15
- Feeding *see* Nutrition
- Felty's syndrome, 121–122, 122–125, 140
- Femoral head, avascular necrosis, 90
- Fentanyl, 376
- Ferritin, 79
- Fever of unknown origin (FUO) *see* Pyrexia of unknown origin (PUO)
- Fibrinogen degradation products (FDPs), 110
- Fibrinolytic therapy, 170
- Fifth's disease, 146
- Filgrastim (G-CSF), 378
- Fingolimod, 482
- Fits/faints, 496–503
associations, 497
case history, 496–498
diagnosis, 498
epilepsy, 498
features, 496–499, 497
investigations, 496
management, 498
see also Syncope
- Flecainide, 276
- Flenley acid-base nomogram, 340
- Flexi sigmoidoscopy, 53–54
- Flucloxacillin, 17, 221, 353, 542
- Fluconazole, 378
- Fludarabine, 86
- Fluid balance/electrolytes, 223–227
assessment, 223–227, 224, 225
case history, 225–226
investigations, 225
management, 226–227, 226, 227
sodium problems, 227–228
- Fluid replacement, 232
management, 415–416, 416
- Fluids, dialysis, 254
- Folate (folic acid) deficiency, 81, 82
causes, 81–82, 140
depression, 525
treatment, 83
- Folinic acid, 83
- Fomepizole, 397
- Food bolus obstruction, 35
- Food poisoning, 11–13
- 4S trial, 302
- Frequency, defined, 260–261
- Friedreich's sign, 202–203
- Fulminant meningococcaemia, 7
management, 7
- Functional bowel disease, 55
case history, 55
investigations, 55
management, 55
- Fungal pneumonia, 355
- Fungi, 562
- Furosemide, 65, 187, 187, 240, 387, 433, 513
heart failure, 297, 439
respiratory conditions, 234, 343, 377
- Fusidic acid, 221, 353
- Fusion beats, 272

G

- Galantamine, 158, 158, 519
 Gallstones, 60, 75
 case history, 63
 Gamma-butyric acid, 515
 Gammahydroxybutyric acid
 (GHB) abuse, 407
 features, 407
 investigations, 407
 treatment, 407
 Gastrointestinal (GI) bleeding, 67
 causes, 67, 68
 management, 68–69, 68–69
 Gastrointestinal (GI) drugs, 515
 Gastro-oesophageal reflux disease
 (GORD), 45–46
 case history, 45
 features, 45
 investigations, 45, 45
 management, 46
 Gaviscon, 46
 Gentamicin, 7, 311, 377, 494
 pneumonia, 353, 356
 septicaemia, 6
 Geriatric Depression Scale, 159,
 160, 163
 Gestational diabetes, 429–430
 Giant cell arteritis *see* Cranial
 arteritis
 Giardiasis, 39
Ginkgo biloba, 158
 Glandular fever, 63, 97–98,
 146–147
 Glasgow Coma Scale (GCS), 390,
 405, 482, 486, 487, 501
 Glatiramer acetate, 482
 Gliclazide, 187, 187
 Glomerulonephritis *see* Acute
 glomerulonephritis (GN)
 Glucocorticoids, 449
 Glucose, 291, 456
 Glucose-6-phosphate
 dehydrogenase (G6PD)
 deficiency, 100–105
 case history, 101
 defined, 100–103
 diagnosis, 103–104
 differential diagnosis, 101–103,
 102–103
 investigations, 101
 treatment, 104–105
 Glycerol suppositories, 37
 Glyceril trinitrate, 187, 387, 433

- Goitres, 435
 Goodpasture's disease, 253
 Gout, 209–211
 pseudo-gout, 211, 211
 treatment, 256
 Granisetron, 505
 Granulation, 144
Granulicatella spp, 310
 Granulocytes, immature, 144
 Guillain-Barré syndrome, 506–507
 case history, 506
 diagnosis, 506
 investigations, 506
 management, 506–507
 prognosis, 507

H

- H₂ antagonists, 515
 HACEK group species, 310
 Haematemesis/melaena, 66–69,
 385
 case history, 66
 causes of bleeding, 67
 resuscitation, 66–69
 Haematological oncology, 131–140
 assessment, 134–135
 case history, 131–133, 135–136
 diagnosis, 135
 differential diagnosis, 138, 139
 disease groups, 131–138
 features, 138
 investigations, 133, 135–136
 Haematuria, without albuminuria,
 259–260
 causes, 259–260
 examination, 260
 history taking, 259–260
 investigations, 260
 Haemoglobin, elevated *see*
 Polycythaemia (PV)
 Haemolysis, 102, 103
 acute, 102, 105
 causes, 105
 intravascular, 104, 104
 Haemolytic anaemia, 83–92
 autoimmune *see* Autoimmune
 haemolytic anaemia (AIHA)
 case history, 83–84
 chronic, 147
 features, 85
 investigations, 85
 microangiopathic (MAHA), 143
 red cells, 84–86

- Haemolytic transfusion reaction, 127–129
- Haemolytic uraemic syndrome (HUS), 12, 13
- Haemophilia, 106–107
- Haemophilus* spp, 310, 494
- Haemophilus influenzae*, 23, 125, 345, 350, 495
- Haemoptysis, 333–336
 case history, 333
 causes, 333–336
 management, 334–336, 335, 335
 massive, 335–336, 336
- Haemorrhage, management, 130
- Haemostasis, failure, 130
 causes, 130
 investigations, 130
- Hairy leucoplakia, 562–563
- Hallpike's test, 470, 470, 470
- Hallucinations/illusions, 509
- HALO system, 46
- Haloperidol, 88, 519, 539
 delirium, 156, 512, 516
- Head injury
 associated problems, 488
 case history, 489
 follow up, 488–489
 management, 488
 NICE guidelines, 489
- Headaches, 501–502
 causes, 503, 504
 chronic, 504
 episodic, 504
 sudden, 504
- Heart block, 300
- Heart disease, elderly, 172–177
 case history, 172
 investigations, 172–173
- Heart failure, 243, 303–306
 acute *see* Acute heart failure
 case history, 303–304
 investigations, 303–304
 lifestyle changes, 305
 management, 304–305
 precipitating factors, 304
 prosthetic valves, 309
 treatment, 439–440
- 'Heat rash' (miliaria), 549
- Heimlich manoeuvre, 326
- Helicobacter pylori*, 46–48, 301, 390
 peptic ulcer disease, 48, 49
- Heparin, 118, 209, 368–369, 433, 476
 bleeding disorders, 111–112
 thrombosis, 118, 286, 323
- Heparin-induced
 thrombocytopenia with
 thrombosis (HIT), 121
- Hepatic encephalopathy, 62
- Hepatitis A virus (HAV), 58, 63
- Hepatitis B virus (HBV), 58, 58
- Hepatitis C virus (HCV), 57–59, 58
- Hepatocellular damage, 61
 investigations, 62–63
 management, 61–62
- Hereditary angio-oedema (HAE), 547–548, 548
- Hereditary non-polyposis colon cancer (HNPCC), 54, 54
- Hernia repair, 115–116
- Heroin, 534, 536
- Herpes, ophthalmic, 18
- Herpes simplex virus type 1 (HSV1) encephalitis, 483–484
- Hibernating myocardium, 295
- Hiccups, 33–34
 case history, 33
 causes, 34
 investigations, 33
- Highly active anti-retroviral therapy (HAART), 21–23
- Hip, osteoarthritis (OA), 191–196, 192
- Histoplasma* spp, 562
- Histoplasma capsulatum*, 23
- HIV/AIDS, 21–25, 147, 220
 assessment, 24
 case history, 21
 chest conditions, 22–23
 cutaneous infections, 562
 diagnosis, 21
 malignancy, 23–24, 563
 opportunistic infections, 562
 skin reactions, 559–564
 treatment, 25
- HIV-associated nephropathy (HIVAN), 258, 258
- Hives *see* Urticaria
- HOPE trial, 301–302
- Hormone replacement therapy (HRT), 217
- Hospital-acquired pneumonia *see* Severe hospital-acquired pneumonia (SHAP)

- Hot joint *see* Acute hot joint
- Humerus, osteomyelitis, 90
- Hydrocortisone, 40, 438, 547, 563
 Addison's disease, 444, 446
 hypopituitarism, 456, 456
 respiratory conditions, 343, 348
 surgery, 445
- Hydroxocobalamin, 82–83
- Hydroxycarbamide, 88, 100
- Hydroxyurea, 564
- Hydroxyzine, 88, 547, 563–564
- Hyoscine, 44
- Hypercalcaemia, 377, 446–448
 case history, 446
 causes, 447
 features, 447
 investigations, 446–447
 management, 446
 metabolic, 379
- Hyperglycaemia, 415
- Hyperkalaemia, 238–241
 case history, 238
 causes, 239–240, 239, 241
 management, 241
 potassium, 239–241, 240
- Hyperketonaemia, 415
- Hyperkinetic movement
 disorders, 505–506
- Hypernatraemia, 227, 227, 229–230
 case history, 229
 treatment, 229, 230
- Hyperosmolar hyperglycaemic
 state, 416, 418–420
 assessment, 419
 case history, 418
 investigations, 419
 management, 418–420
 presentation, 418–419
- Hyperparathyroidism, 250
 biochemical features, 447–448
 treatment, 448
- Hypersplenism, 122, 122
 pathophysiology, 123–125
- Hypertension (HT), 171, 238, 249
 assessment, 317–318
 case history, 317, 320
 causes, 318–319
 drugs, side effects, 321–323
 investigations, 319–320, 319,
 320
 management, 320
 pulmonary *see* Pulmonary
 hypertension
- signs, 318–319
 treatment, 321
 venous, 542
- Hyperthyroidism, 432–433
 case history, 432, 434, 434
 causes, 435
 elderly, 433–434, 434
 investigations, 433, 433, 435
 treatment, 433, 435–437, 436
- Hypertrophic cardiomyopathy
 (HCM), 316
 vs aortic stenosis (AS), 317,
 318
 practice points, 316–317
- Hyperventilation, 332–333
 case history, 332
 syncope, 266
 syndrome, 333
- Hypocalcaemia, 449–451
 assessment, 450
 case history, 449
 causes, 450–451
 features, 449–450
 investigations, 450
 management, 449, 451, 451
- Hypoglycaemic coma, 420–422,
 421
 assessment, 421
 case history, 420
 causes, 422
 investigations, 421
 management, 421–422
 non-diabetic, 422
 presentation, 420, 421
- Hypokinetic movement disorders,
 505
- Hyponatraemia, 224, 227, 227,
 459
 case history, 228
 causes, 228, 460
 investigations, 460
 management, 228
 treatment, 460
- Hypoparathyroidism, 452
- Hypopituitarism, 454–457
 assessment, 455, 457
 case history, 455
 causes, 457
 features, 455
 investigations, 455, 457
 management, 456, 456
 pathophysiology, 454–455
 presentation, 457

- Hyposplenism, 123–125
see also Overwhelming
 post-splenectomy infection
 (OPSI)
- Hypotension
 cardiogenic, 387
 hypovolaemic, 388
 intubation, 344
 orthostatic, 151–152, 266
 postural, 152
 treatment, 501
- Hypothalamic-pituitary-adrenal
 axis, 445
- Hypothalamic-pituitary-thyroid
 axis, 436
- Hypothermia, 175–177
 case history, 176
 causes, 176
 features, 176, 177
 investigations, 176
 management, 176–177
- Hypothyroidism, 440–442
 case history, 440, 441
 compensated, 442
 treatment, 441–442
- Hypovolaemic hypotension, 388
- Hypovolaemic shock, 129, 231
 arterial blood gas (ABG), 387
 case history, 383
 causes, 385
- Hypoxaemia, 339, 343
- I**
- Ibuprofen, 88, 183, 198, 467, 535
- Icatibant, 548
- Idiopathic intracranial
 hypertension (IIH), 464
 management, 465
 precipitating factors, 465
- Idiopathic thrombocytopenic
 purpura (ITP), 113
 diagnosis, 113
 management, 114
- Illusions, 509
- Immune reconstitution
 inflammatory syndrome
 (IRIS), 23
- Immunoglobulin, 547
- Incontinence *see* Urinary tract
 infection (UTI)
- Industrial chemicals, 515
- Infection, 144–147, 254–255, 309,
 532
- Infectious diseases, 1–19
- Infectious mononucleosis, 553,
 554
- Infective endocarditis, 309–312
 case history, 309
 Duke criteria, 310
 investigations, 311
 practical considerations,
 311–312
- Inflammatory autoimmune
 vasculitis, 251–253
- Inflammatory bowel disease (IBD),
 39
 investigations, 39–40
 manifestations, 42
- Inflammatory disorders, iron
 status, 141–142
- Infliximab, 40, 199
- Influenza, viral, 350
- Inhalation pneumonia, 355
- Inherited bleeding disorders,
 105–106, 106–107
- Inherited platelet disorder
 diagnosis, 116
 management, 116
- Inherited thrombocytopenia, 113
- Injectable adrenaline pens, 547
- Insect stings/bites, 408
- Insulin
 intravenous/subcutaneous, 424
 management, 417
 surgery, 426
- INTERCEPT trial, 301
- Intercostal tube insertion, 371–372
- Interferons, 515
- Interpersonal skills, 538–539
- Intra-aortic balloon pump (IABP),
 293
- Intramuscular medication, 512
- Intubation, 344
- Iodine, 440
- Ipratropium, 330
- Irinotecan, 376–377
- Iron deficiency anaemia, 50–52, 80
 case history, 50
 causes, 80
 investigations, 50–52, 51
 treatment, 80
- Iron status, inflammatory
 disorders, 141–142
- Ischaemic heart disease, 302, 316
- Ischaemic stroke, 472, 473
- Isoniazid, 218, 358–362, 496

- Isotretinoin, 564
 Itchy folliculitis, 564
- J**
 Jaundice, 59–63
 case history, 59–61
 investigations, 59, 60, 61
- K**
 Kaposi's sarcoma (KS), 23, 561, 563
 Ketamine, 515
 Ketones, 418
 Kidney disease
 acute *see* Acute kidney failure
 chronic *see* Chronic kidney disease (CKD)
 injury *see* Acute kidney injury
 presentation, 223
Kingella kingae, 310
Klebsiella spp, 350
 Knee aspiration, 219
 see also Chondrocalcinosis of knee
- L**
 β -lactamase inhibitor, penicillin with, 6
 Lactate levels, 387
 Laxatives, 88
 Left pleural effusion, 364, 365
 Left ventricular failure (LVF), 303, 328
Legionella spp, 310, 350
 Legionnaire's disease, 353
 Legs, weakness, 377
 Leg ulcers, 542–543
 causes, 542
 investigations, 542
 management, 543
 see also Swollen red leg; Swollen/painful leg
 Leucoerythroblastic anaemia, 143–144
 Leukaemia, 131
 vs lymphoma, 138, 139
 see also Acute leukaemias
 Levodopa (LD), 185, 478, 478, 514
 Levothyroxine, 162–163, 441, 456
 Lewy body dementia, 158
 Libman–Sacks endocarditis, 208–209
 Lichen planus, management, 552
 Lichenoid eruptions, 558
 Lidocaine, 183, 513
 Life support
 advanced, algorithm, 282
 basic ABCDE, 280–281, 281
 Lipid-lowering drugs, 302
 Lipodermatosclerosis, 541
 Lisinopril, 323, 513
Listeria meningitis, 494, 495
 Lithium, 514
 Liver abscess, 3
 treatment, 3–4
 Liver biochemistry, abnormal, 57–66
 case history, 57
 investigations, 57–59, 58
 Liver disease
 anaemia, 141–142
 bleeding, 108
 see also Acute liver disease
 Liver failure, 70–71
 case history, 70
 management, 70–71
 signs, 70
 Liver function tests, 57, 58
 Lobar pneumonia, 351
 Locked-in syndrome, 490–491, 492
 Loperamide, 535
 Loratidine, 547
 Lorazepam, 156, 499, 532, 539
 Low molecular weight heparin (LMWH), 286, 289–290, 297, 368, 507
 Lumbar puncture, 493, 501
 indications/contraindications, 494
 Lung abscess, 357–358
 case history, 357, 357
 diagnosis, 358
 differential diagnosis, 357–358
 Lung cancer
 investigations, 373, 374–375, 379
 small cell (SCLC), 376–377, 376
 non-small cell (NSCLC), 376
 Lung disease
 aspergilloma, 334
 intrinsic, 339
 polycythaemia, 94, 96
 Lungs, venous congestion, 334
 Lupus nephritis, treatment, 258

- Lymphomas, 131, 563
 high-grade, 138
 vs leukaemia, 138, 139
 Lysergic acid (LSD), 515
- M**
- Macrocytic anaemia
 case history, 80–81
 causes, 81–83
 diagnosis, 82
 investigations, 80–81, 82–83
 management, 82–83
- Macropapular rash, 553, 554
- Macroscopic haematuria, 259
- Maculopapular eruptions,
 555–557, 558
- Magnesium sulphate, 37, 274, 331
- Malaria, 16, 101, 103, 145–146
 features of falciparum malaria,
 145–146
 management, 16
- Malignancy, HIV/AIDS, 23–24,
 563
- Malignant melanoma, 563
- Malignant pleural effusion,
 363–364
- Malnutrition Universal Screening
 Tool (MUST), 28
- Mannitol, 474, 488
- Mefloquine, 514
- Megaloblastic anaemia, 81
- Meggitt–Wagner classification,
 diabetic foot ulcers, 428
- Melaena *see* Haematemesis/
 melaena
- Melkersson–Rosenthal syndrome,
 469
- Memantine, 158, 158, 519
- Membranous nephropathy,
 treatment, 258
- Meningitis, 491–493
 case history, 491, 495
 causes, 493–496
 diagnosis, 493
 investigations, 491, 491, 493, 495
 treatment, 494
- Meningococcal meningitis, 7–9,
 491, 494
 case history, 7, 7
 causes, 494–495
 chemoprophylaxis, 8–9, 9
 diagnosis, 7
 investigations, 8
- Meningococcal septicaemia, 113
- Meningoencephalitis, causes, 483
- Mental disorders, 528
 organic, 537
- Mental Health Act, 530, 531, 539
- Meptazinol, 216–217
- Metabolic conditions
 acidosis, 340
 alkalosis, 340
 depression, 532
 hypercalcaemia, 379
 syncope, 266
- Metformin, 412–413
- Methadone, 535–536, 535–536
- Methanol, 515
- Methicillin-resistant *Staphylococcus aureus* (MRSA), 6
- Methionine, 397, 402
- Methotrexate, 81, 83, 121–122, 515,
 564
- Methylene blue, 102
- Methylprednisolone, 183, 481, 481
- Metoclopramide, 44, 467, 504–505,
 504
- Metoprolol, 285, 289–290, 299, 301
- Metronidazole, 3, 6, 39–40, 358,
 364
- Miconazole, 563
- Microangiopathic haemolytic
 anaemia (MAHA), 143
- Microcytic anaemia
 case history, 79
 differential diagnosis, 77–79
 investigations, 79
see also Iron deficiency anaemia
- Microscopic haematuria, 259
- Microscopic polyangiitis, 251–253
- Micturation syncope, 265
- Midazolam, 499
- Migraine, 467
 case history, 502
 diagnosis, 502–503
 management, 502
 treatment, 467
- Miliaria, 549
- Milrinone, 295
- Minimal change disease, 258
 treatment, 258
- Mini-Mental State Examination
 (MMSE), 154, 156, 163
- Mirtazapine, 160
- Misoprostol, 183
- Mitoxantrone, 482

- Mitral regurgitation, 308
 Mitral valve disease, 308
 case history, 308
 Mobitz type II second-degree
 heart block, 267
 Modification of diet in renal
 disease (MDRD), 247
 Monoamine oxidase inhibitor
 (MAOI-B), 185, 479
 Mononeuritis (third nerve palsy),
 461
 multiplex, 468, 469
 Monospot test, 19, 97–98
Moraxella catarrhalis, 23
 Morphine, 87, 214, 234, 285
 Movement disorders, 504–506
 case history, 504–505
 diagnosis, 504–505
 hyperkinetic, 505–506
 hypokinetic, 505
 Multidisciplinary approach, 249
 Multidrug-resistant tuberculosis
 (MDRTB), 22
 Multi-infarct dementia, 158
 Multiple myeloma, 507
 diagnosis, 136, 136
 Multiple sclerosis (MS), 480–482,
 500
 case history, 480–481
 investigations, 480–481
 optic neuritis, 480–482
 treatment, 481–482
 Multisystem vasculitis, 251–253
 diagnosis, 252, 253
 Murmurs, prosthetic valves, 309
 Musculoskeletal conditions, 337
 Myasthenia gravis
 case history, 463
 investigations, 463
 Mycobacteria tuberculosis (MTB),
 22–23
 treatment, 22–23
Mycobacterium tuberculosis
 case history, 361–362
 key points, 362
 treatment, 362
Mycobacterium avium intracellulare,
 220, 362
 Mycoplasma pneumonia N.B.,
 treatment, 353
Mycoplasma spp, 345, 350
 Mydriatics, 514
 Myelodysplasia (MDS), 140
 Myeloma, 131
 multiple, diagnosis, 136, 136
 Myeloproliferative disorder, 99,
 100
 Myocardial infarction (MI)
 acute, 172–173, 173, 288–289
 defined, 288
 high-risk survivors, 302
 management, 289–290
 secondary prevention, 301–302
 shock, 385
 Myocardial infarction (MI),
 ‘silent’, 163
 management, 163
 Myocardial ischaemia
 acute, 291–292
 features, 45
 Myocardial stunning, 295
- N**
- Nalidixic acid, 102
 Naloxone, 390, 536
 Naphthalene, 102, 102, 105
 Naproxen, 467
 Natalizumab, 482
 National Institute for Clinical
 Excellence (NICE) guidelines,
 158, 489
 National Poisons Information
 Service, 396, 400
 National Service Framework
 (NSF) guidelines, 302
 National Stroke Guidelines, 170,
 175
Neisseria meningitidis, 4, 125
 Nephrotic syndrome, 257–259
 case history, 257
 investigations, 257–258
 management, 257
 see also Systemic lupus disease/
 nephrotic syndrome
 Nerve root, 337, 377
 Neurally mediated syndromes,
 268
 Neurological conditions
 coma, 342
 deficits, stroke, 168, 169–170
 depression, 532
 syncope, 266
 Neuropathic ulcers, 542–543
 Neutropenia
 investigations, 377
 management, 377–378

- Neutrophil leucocytosis, 144, 144
 Nickolsky sign, 557
 Nifedipine, 301, 321
 Nimodipine, 501
 Niridazol, 102
 Nitrates, 297, 304
 Nitrazepam, 514
 Nitrofurantoin, 102
Nocardia asteroides, 23
 Non-dihydropyridines, 301
 Non-Hodgkin's lymphoma (NHL), 24, 139
 Non-infective meningitis, 494
 Non-invasive ventilation (NIV), 305, 343–344, 344
 Non-small cell lung cancer (NSCLC), 376
 Non-specific illness, elderly, 161–172
 case history, 161–162
 Non-ST elevation MI (NSTEMI), 291, 292
 Non-steroidal antiinflammatory drugs (NSAIDs), 44, 88, 183, 188, 467
 rheumatology, 196, 198, 217
 side effects, 515
 Non-tuberculous (atypical) mycobacteria, 562
 Norton Scale, pressure ulcers, 179
 Nutrition, 27–30
 assessment, 27, 28
 case history, 27
 enteral feeding, 29, 29
 parenteral feeding, 27, 27, 29–30
 patient selection, 27–29
- O**
- Ocular lesions, sarcoidosis, 379
 Oculogyric crises, 504–505
 treatment, 505
 Oesophageal cancer, 35, 36
 management, 36
 Oesophageal conditions, 337
 rupture, 337
 varicies, 68, 68–69
 Oestrogen, 456
 Olanzapine, 156, 540
 Oliguria, 230
 Omeprazole, 46, 196
 Oncology *see* Haematological oncology
 Ondansetron, 505
- Ophthalmic herpes, 18
 Opiates, 376
 Opiate dependence, 534–537
 assessment, 534–535
 case history, 534, 536
 effects, 534
 investigations, 535
 management, 535–537
 withdrawal symptoms, 535–536
 Optic neuritis, 480–482
 Oral contraceptive pill, 207
 Orthostatic hypotension, 151–152, 266
 Osmolality, calculation, 418
 Osteoarthritis (OA), 191–196
 assessment, 191, 192–194
 case history, 191
 diagnosis, 191, 195
 examination, 191–195
 features, 191–196, 192
 hospitalisation, 195–196
 treatment, 196
 Osteomyelitis, 218–219
 case history, 218
 differential diagnosis, 218–219
 humerus, 90
 investigations, 218
 Osteopenia, 216
 Osteoporosis, 215–217
 case history, 215
 differential diagnosis, 215–216, 216
 investigations, 215
 management, 216–217
 Ovarian malignancy, 64
 Overwhelming post-splenectomy infection (OPSI), 125
 major pathogens, 125
 pathophysiology, 125
 prevention, 125
 Oxygen dissociation curve, 342
- P**
- Pacemakers, 277–312
 classification, 278
 common, 278
 post-MI, 300
 problems, 278–279
 Pamaquine, 103
 Pamidronate, 377
 Pancreatitis, acute, 44, 45
 Papilloedema palsies, case history, 464

- 'Papulo-squamous' dermatoses, 563–564
- Paracentesis (ascitic tap), 64
- Paracetamol, 44, 88, 169, 467
- Paracetamol poisoning, 62–63, 398–402
 - antidotes, 401–402
 - case history, 398, 528
 - examination, 399, 400
 - management, 399–400, 401
 - treatment, 402
- Parenteral nutrition, 27, 27, 29–30
- Parkinson's disease (PD), 184–185, 478–479
 - case history, 184, 478
 - diagnosis, 184, 185
 - differential diagnosis, 184–185
 - features, 184–185
 - management, 185
- Paroxysmal hemicrania, case history, 503
- Partial left lateral medullary syndrome, 472
 - case history, 472
- Patient controlled analgesia (PCA), 87–88
- Patient wishes, cardiopulmonary resuscitation (CPR), 188–189
- Pegylated interferon, 59
- Penicillin, 19, 311, 491, 494, 542
 - with β -lactamase inhibitor, 6
- Pentamidine, 22
- Peptic ulcer disease, 46–49
 - alarm features, 47
 - case history, 48–49
 - history taking, 46–47
 - hospital discharge, 49
 - investigations, 47–49
 - stigmata, 49
 - treatment, 48
- Pericarditis, 287, 287, 336
- Peripheral neuropathy, 71
- Peripheral nutrition, 29
- Peripheral vestibular lesions, 470
- Pernicious anaemia (PA), 83, 140
- Persecutory delusions, 510
- Personality factors, 538
- pH, 241–242, 242
- Phaeochromocytoma (catecholamine crisis), 452–454
 - associations, 453
 - case history, 452, 453
 - diagnostic tests, 454
 - management, 454
 - presentation, 452–453
- Phencyclidine, 515
- Phenobarbital, 499, 556
- Phenothiazines, 156, 512, 514
- Phenoxybenzamine, 454
- Phenytoin, 499, 556
- Philadelphia chromosome, 137
- Philadelphia Geriatric Center Morale Scale, 163, 166
- Photosensitivity, 556, 556, 558
- Physical illness, 538
- Physical urticaria, 546
- Pigmentation, drugs, 555
- Piperacillin, 389, 392–393
- Pituitary apoplexy, 455
- Plant alkaloids, 515
- Plasma D-dimers, 367, 367
- Plasmodium falciparum*, 16, 145
- Platelet count, elevated, 98–116
 - case history, 98
 - causes, 98–100
 - complications, 100
 - investigations, 99
 - management, 100
- Platelet disorders, 112–115
 - case history, 112–113, 115–116
 - inherited, 116
 - investigations, 112–113
- Pleural effusion, 363–366, 373, 379
 - case history, 363–364, 365
 - causes, 364–365
 - investigations, 363–364
 - management, 364
 - signs, 363
 - treatment, 364
- Pleurisy, 337
- Pneumococcal meningitis, 493–494, 494
- Pneumococcal sepsis, 123–124, 124
- Pneumocystis jiroveci* pneumonia, 21, 354
 - case history, 354, 354
 - treatment, 22, 355
- Pneumonia, 350–357, 360, 374–376
 - case history, 360
 - community-acquired *see* Community-acquired pneumonia
 - hospital-acquired *see* Severe hospital-acquired pneumonia (SHAP)

- investigations, 360–361, 361
- lobar, 351
- severe, 341
- types, 355
- see also Pneumocystis jiroveci pneumonia*
- Pneumothorax, 369–372
 - case history, 369–370, 370
 - causes, 369–372
 - diagnosis, 369, 371
 - differential diagnosis, 370–371
 - management, 369–372
- Poisoning, 395–410
 - poison-induced delirium, 515
- Polycythaemia, 92–96
 - apparent/relative, 93, 94, 95
 - case history, 92–93
 - causes, 93–96, 93
 - diagnosis, 94–95, 95
 - investigations, 94–95
 - management, 93–94, 96
 - secondary, 95
- Polycythaemia vera (PV), 94–95, 95
 - complications, 96
 - features, 95, 96
- Polymorphic light eruption, 549
- Polymyalgia rheumatica (PMR), 212–213
- Portosystemic encephalopathy (PSE), 70
- Post-herpetic neuralgia, 18
- Postural hypotension, 152
- Potassium, 239–241, 240
 - replacement, 417, 417
- Potassium iodide, 438
- Pott's disease, 218
- Pramipexole, 185, 479
- Prasugrel, 301
- Pravastatin, 302
- Prednisolone, 19, 40, 187, 212, 445
 - dermatology, 547, 550
 - neurology, 468, 496
 - respiratory conditions, 345, 348
 - rheumatology, 200, 217
- Pregnancy, diabetes mellitus, 429–439
 - case history, 429–430
 - management, 429–430
- Pressure ulcers, 177–179
 - assessment, 178
 - case history, 177
 - causes, 178
 - investigations, 178, 178
 - management, 178–179
 - risk factors, 177–179
- 'Prickly heat', 549
- Primaquine, 102, 102
- Primary pulmonary artery hypertension, 314
- Primidone, 556
- Probenecid, 102
- Prochlorperazine, 44, 88
- Proctoscopy, 53
- Procyclidine, 505, 512
- Progesterone, 456
- Progressive supranuclear palsy (PSP) (Steele–Richardson syndrome), 485, 485
- Propofol, 499
- Propranolol, 301, 433, 435, 438, 454, 513
- Propylthiouracil (PTU), 435, 438
- Prosthetic valves, 309
- Pruritic papular eruption (PPE), 564
- Pruritus, 551–553
 - case history, 551
 - causes, 552
 - investigations, 553
 - treatment, 563–564
- Pseudodementia, 516
- Pseudo-gout, 209–211, 211
 - management, 211
- Pseudomembranous colitis, 11–16
 - case history, 10
 - differential diagnosis, 10
 - investigations, 10
 - management, 11
 - prevention, 11
 - questions, 10
- Pseudomonas* spp, 6, 350, 392–393, 495
- Psittacosis, 353–354
- Psoriasis, 564
 - management, 552
- Psychiatric disorders, 537
- Psychiatric liaison referral, 530
- Psychological conditions, 533
- Pulmonary embolism (PE), 366–369
 - associated conditions, 366–367
 - case history, 366
 - diagnosis, 366
 - haemoptysis, 334

- investigations, 367–368
 - treatment, 368–369
 - Pulmonary haemorrhage, 252, 334
 - Pulmonary hypertension, 312–314
 - case history, 312, 314
 - diagnosis, 314
 - investigations, 312
 - see also* Cor pulmonale
 - Pulmonary oedema, 432
 - acute, 172, 173
 - flash, 233–238
 - Pulmonary sarcoidosis, 380
 - Pulmonary tuberculosis, 334
 - Pulse patterns, valvular heart disease, 307
 - Pyoderma gangrenosum, 43
 - Pyogenic abscess, 358
 - Pyogenic streptococci, 4
 - Pyrazinamide, 22–23, 218, 358–362
 - Pyrexia of unknown origin (PUO), 1–4, 358
 - case study, 1
 - causes, 2
 - defined, 1–4
 - investigations, 2–3, 2–3
 - management, 1
 - questions, 1
 - Pyrimethamine, 16, 22
- Q**
- Q fever, 353–354
 - Quality of life, 189
 - Quinine sulfate, 16
 - Quinolone, 5, 102
- R**
- Radioiodine, 436
 - Raloxifene, 217
 - Ramipril, 297–298, 301–302
 - Ramsay Hunt syndrome, 18, 468
 - Rasagiline, 479
 - Rash/eruption, generalised, 550–553
 - case history, 550
 - complications, 550–551
 - differential diagnosis, 550
 - history taking, 550–551
 - HIV/AIDS, 561–562
 - investigations, 551
 - management, 551
 - see also* Cutaneous adverse drug reactions (ADR); Sun-induced rash
 - Reactive arthritis, features, 220
 - Recombinant human growth hormone, 456
 - Recreational drugs, 515
 - Rectal bleeding, 52–54
 - case history, 52
 - investigations, 53
 - management, 52–53
 - Recurrent meningitis, 494
 - Red blood cells, 84–86, 92
 - Re-entrant tachycardia, 270
 - Referred pain, 337–338
 - Reiter's disease, 219
 - Renal disease, 109
 - Renal failure, 109, 295
 - Renal tract imaging, 246, 246
 - Renal transplants, 256
 - monitoring, 256–257, 256
 - Renal unit referral, 246
 - Renal/ureteric colic, 262–264
 - case history, 262
 - causes, 262
 - diagnosis, 262–264
 - examination, 263
 - history taking, 262–263
 - investigations, 263, 263–264
 - management, 263
 - Renin-angiotensin-aldosterone system, 322
 - Renoprotection, 250
 - Renovascular disease, 234–235, 235–237
 - atheromatous, 238
 - investigations, 238
 - management, 236
 - Replacement therapy, hypopituitarism, 455, 456
 - Respiratory conditions
 - acidosis, 339, 343
 - alkalosis, 340
 - HIV/AIDS, 22–23
 - management, 24
 - Respiratory failure, 338–344, 348
 - acid-base changes, 339–340, 340
 - arterial blood gas (ABG)
 - sampling, 339, 339, 341, 341, 343–344
 - case history, 343
 - diagnosis, 339
 - investigations, 339, 339, 343–344
 - key points, 348–349
 - management, 341
 - mechanical ventilation, 344

- sarcoidosis, 381
 signs, 341–342
 treatment, 342, 342, 348
- Respiratory support, poisoning, 396
- Resuscitation
 do not attempt (DNAR), 188–189, 189
 haematemesis/melaena, 66–69
see also Cardiopulmonary resuscitation (CPR)
- Returning traveller, 14–16
 case history, 14
 diagnosis, 16
 diarrhoea, 38
 differential diagnosis, 15
 investigations, 15–16, 15
 questions, 14–16
- Revascularisation, 292, 298
- Rhabdomyolysis, 243
- Rheumatoid arthritis (RA), 121–122, 197–200
 case history, 197
 differential diagnosis, 197–200
 investigations, 198, 198
 management, 197–198
 manifestations, 199–200, 199
- Rib erosion, 373
- Ribavirin, 59
- Rifampicin, 9, 218
 tuberculosis, 22–23, 358–362, 496
- Right ventricular infarction, 295–297
 case history, 272–273, 295–296
- Right-sided endocarditis, 312
- Risedronate, 217
- Risperidone, 512
- Rituximab, 86
- Rivastigmine, 158, 158, 519
- Rizatriptan, 467
- Romiplostim, 115
- Ropinirole, 185, 479
- Rotigotine, 479
- Rouleaux, 142
- Royal College of Physicians, 163
- S**
- Salbutamol, 345, 348
- Salicylate overdose, 402–404
 case history, 402–403
 features, 403
 treatment, 403
- Salmon calcitonin, 216–217
- Salmonella* spp, 13
- Salmonella typhi*, 13–14
- Sarcoidosis, 378–381, 379, 545
 case history, 378, 380
 defined, 379–381
 investigations, 380
 presentation, 378–381
- Scabies, 552–553, 562
- Schizophrenia, 540
- Scopolamine, 514
- Seborrhoeic dermatitis, 561, 563
- Sedatives, 515
- Sedative withdrawal
 presentation, 516
 treatment, 516
- Seizures
 atonic, 498
 treatment, 498–499
- Selective oestrogen-receptor modulator (SERM), 217
- Selective serotonin reuptake inhibitors (SSRIs), 527
- Selegiline, 185, 479
- Self-harm *see* Deliberate self-harm (DSH)
- Self-poisoning, 395–398
 assessment, 395
 case history, 395
 investigations, 395
 management, 396–398
- Sengstaken–Blakemore tube, 69
- Sepsis, 144–147, 243
- Septic arthritis, 219–221
 case history, 219
 investigations/management, 219–221, 219, 220, 221
- Septic shock, 5, 231
 case history, 388
 causes, 385, 388
 management, 386, 389
 pathophysiology, 389
- Septicaemia, 4–9
 case history, 4
 causes, 4
 differential diagnosis, 5
 investigations, 5
 management, 5–6
 meningococcal meningitis, 7–9
 predisposing factors, 4, 5
- Serum creatinine, 234
- Serum transferrin receptor assay, 79
- VII nerve lesion *see* Bell's palsy

- Severe acute asthma, 330
 case history, 329
 intensive care, 331
 life-threatening, 331, 341
 management, 330–331
 treatment, 331–332
- Severe brain injury, 488, 489–491
 case history, 489–491
 differential diagnosis, 492
 examination, 490
 investigations, 490
 prognosis, 490
- Severe hospital-acquired pneumonia (SHAP), 350
 bacteriology, 356
 case history, 355–356
 diagnosis, 356
 investigations, 356
 management, 356–357
- Severe hypercalcaemia, 448–449
 case history, 448
 management, 449
- Sexually transmitted infections (STIs), 15, 21–25
- Shigella* spp, 13
- Shingles, 16–18
 case history, 16
 investigations, 17
 management, 17
 secondary infection, 17
- Shock, 68, 383–390
 cardiogenic *see* Cardiogenic shock
 causes, 384–385
 diagnosis, 385
 examination, 385–387
 hypovolaemic *see* Hypovolaemic shock
 investigations, 385, 387
 management, 386
 physiology, 384, 384
 septic *see* Septic shock
 treatment, 387–388
- SHOCK trial, 293
- Shy-Drager parkinsonism, 185
- Sick sinus syndrome, 150
- Sickle-cell disease (SCD), 86–89
 anaemia, 123–124, 124
 case history, 86
 complications, 89, 89, 90
 diagnosis, 91, 91–92
 investigations, 86
 questions, 86–87
 treatment, 87–89
 types, 44
- Sixth nerve palsy, 464, 465
- Skin condition, 170
 cancers, 563
 lesions, sarcoidosis, 379
 reactions, 542, 555
- Small bowel obstruction, 32, 33
 differential diagnosis, 32
 management, 32
- Small cell lung cancer (SCLC), 376–377, 376
- Smoking, 172
- Sodium problems, 227–228
- Sodium urate, 209
- Solitary nodules, 437
- Solvents, 515
- Somatostatin, 69
- Sotalol, 274, 277
- Speech and Language Therapist (SALT), 171
- Spinal cord compression, 500, 500, 507
 case history, 507
 diagnosis, 508
 investigations, 507
- Spinal tuberculous osteomyelitis, 218
- Spirometry, 346
- Spirolactone, 65, 305, 513
- Spleen, size, 122
- Splenectomy, 123
see also Overwhelming post-splenectomy infection (OPSI)
- Splenomegaly, 121–125
 case history, 121–124
 causes, 122, 122
- Squamous cell carcinoma, 36, 334
- ST elevation myocardial infarction (STEMI), 285, 287, 291–292
 diabetes mellitus, 423, 424
 management, 285–286
- Stanozolol, 548
- Staphylococcal pneumonia, treatment, 353
- Staphylococcus aureus*, 4, 17, 218, 495
 community-acquired pneumonia (CAP), 350, 352
 septic arthritis, 220–221
- Statins, 172, 175, 291, 302
- Status epilepticus, 498

- Steele–Richardson syndrome, 485, 485
- Steele–Richardson–Olszewski parkinsonism, 185
- Steroids, 19, 40, 187, 343, 444–446, 507
 case history, 444
 cranial (giant cell) arteritis, 213
 dermatology, 544, 564
- Stevens–Johnson syndrome (SJS), 557
 /toxic epidermal necrolysis (SJS/TEN) overlap, 557, 560
- Stings/bites, insect, 408
- Stone formation, 263–264, 263–264
- Streptococci, Group A, 4
Streptococcus bovis, 310
Streptococcus pneumoniae, 4, 23, 87, 123–124, 124–125, 345, 350
Streptococcus pyogenes, 17, 19
Streptococcus viridans, 311
- Stridor, 377
 causes, 329
 upper airway obstruction with, 328
- Stroke, 163–172, 472–474
 case history, 167, 473
 causes, 167, 476–477
 diagnosis, 169
 investigations, 170, 171, 473–474, 473, 478
 management, 169–171, 474
 pathology, 167
 pathophysiology, 472
 prognosis, 171
 questions, 167
 risk factors, 171
 secondary prevention, 171–172
 signs, 167–169, 168
see also Transient ischaemic attack (TIA)
- Subarachnoid haemorrhage
 case history, 501
 diagnosis, 501–502
- Subdural haemorrhage, 477–479
 case history, 477
 diagnosis, 477–478, 480
 management, 477–478
- Sublingual glyceryl trinitrate (GTN), 285
- Subphrenic abscess, 33
 treatment, 33–34
- Substance use, 537
- Suicide
 increased risk, detection, 528, 529
 prevention, 529
 thoughts, 159, 529
see also Deliberate self-harm (DSH)
- Sulfadoxine, 16
- Sulfasalazine, 102, 554
- Sumatriptan, 467
- Sun-induced rash, 548–550
 case history, 548
 diagnosis, 549–550
 differential diagnosis, 549
 treatment, 549–550
- Superior venacaval obstruction, 377
- Supraventricular tachycardia (SVT), 270
 adenosine, 274
 features, 270, 271
 management, 271–272
- Swallowing difficulty *see* Dysphagia
- Swollen red leg, 541–543
 diagnosis, 541
 differential diagnosis, 541
 examination, 541–542
 investigations, 542
 treatment, 542
- Swollen/painful leg, 323–324
 case history, 323
 causes, 323
- Sympatho-adrenal response, shock, 384
- Syncope, 265–277
 case history, 265–267
 diagnosis, 265, 267–268
 differential diagnosis, 265–266
 investigations, 266–267, 267
 treatment, 268
- Syndrome of inappropriate anti-diuretic hormone (SIADH), 459–460
 case history, 459
 causes, 460
 presentation, 459
- Synovial fluid, 221
- Systemic inflammatory response syndrome (SIRS), defined, 4

- Systemic lupus disease/nephrotic syndrome, 202–206
 case history, 202–203
 diagnosis, 203–206, 204
 investigations, 203–205, 205
 management, 203
 prognosis, 206
- Systemic lupus disease/vasculitis, 200–202
 case history, 200
 diagnosis, 202
 differential diagnosis, 200, 201
 investigations, 200, 201
- Systolic heart failure, 306
- T**
- Tachyarrhythmias *see* Tachycardia
- Tachycardia, 268–274
 case history, 268, 271
 classification, 270
 hospitalisation, 268, 269
 questions, 268
- Tardive dyskinesia
 case history, 505
 diagnosis, 505–506
- Tazobactam, 389
- Temazepam, 519
- Temporal arteritis, 181
- Tension pneumothorax, 371
- Terlipressin, 69
- Testosterone, 456
- Tetany, 333
 causes, 450
- Tetracosactide test, 444
- Tetracycline, 353
- β -thalassaemia trait, 79, 80
- Theophyllines, 348
- Thiamine, 35, 65, 71, 521
- Thiazides, 321, 456
- Thiopentone, 499
- Third nerve palsy, 461, 462
- Thrombocytopenia, 115, 124–125
 causes, 113, 113
 microangiopathic haemolytic anaemia (MAHA), 143–144, 144
 questions, 113
 with thrombosis (HIT), heparin-induced, 121
see also Idiopathic thrombocytopenic purpura (ITP)
- Thrombocytosis, 98, 100
- Thromboembolism, 276
see also Venous thromboembolic disease (VTE)
- Thrombolysis, 286–291, 291, 299, 299
 contraindications, 286
 respiratory disorders, 368, 368
 shock, 387
- Thrombophilia, 117–118, 120, 120
- Thrombosis, 116–131, 206–209
 case history, 116–119, 121, 206
 differential diagnosis, 207, 208
 examination, 206–207
 investigations, 116–121, 117, 207, 208
see also Deep vein thrombosis (DVT)
- Thyroid disorders, 434
- Thyroid function, 439–444
- Thyroid function tests, 434
 interpretation, 441
- Thyroid storm, 438–439
 case history, 438
 treatment, 438–439
- Thyrotoxicosis, 187
- Thyroxine, 84
- Tietze's disease, 337
- Tilt test, 267
- Timolol, 301
- TOE-guided approach, 276
- Toes, erythromelalgia, 96
- Torsade de pointes, 272–273, 272
- Toxic confusional state *see* Delirium
- Toxic epidermal necrolysis (TEN), 555–557
 /Stevens-Johnson syndrome (SJS/TEN) overlap, 557, 560
 treatment, 557–558
- Tranquillising drugs, 512
- Transcobalamin II deficiency, 81
- Transient ischaemic attack (TIA), 174–175, 466, 466, 475–476
 case history, 174, 475
 examination, 174
 history taking, 174
 hospitalisation, 175
 investigations, 174, 475–476

- management, 175
 prognosis, 175
 treatment, 476
- Transjugular intra-hepatic portosystemic shunt (TIPS), 69
- Transplants, 254–257
 case history, 256
 drug interactions, 256
- Trauma
 management, 487
 musculoskeletal, 337
- Traumatic brain injury, 486–493
 case history, 486, 487
 effects/complications, 487–488
- Tricyclic anti-depressants (TCAs), 514, 527
- Tricyclic anti-depressants (TCAs), overdose, 404
 features, 404
 treatment, 404
- Trimethoprim, 7, 181
- Triptans, 467
- Trousseau's sign, 450
- Tuberculosis (TB), 355, 358–363, 376
 case history, 358–360
 investigations, 359, 359
 management, 360
 risk factors, reactivation, 360
- Tuberculosis with meningitis (TBM), 495
 case history, 358
 investigations, 495–496, 495
 management, 496
 treatment, 358–362
- Typhoid, 13–14
 case history, 13
 diagnosis, 14
 investigations, 13
 management, 14
- U**
- Ulcerative colitis, 40, 41, 42
 vs Crohn's disease, 40, 42
 findings, 40
 management, 40, 40
- Ulcers
 venous, 543
see also Diabetic foot; Peptic ulcer disease; Pressure ulcers
- Unconsciousness, causes, 390
- Uncooperative patients, 539
- Unstable angina (UA), 289, 292
 case history, 289
- Upper airway obstruction, 326, 327
 case history, 326
 causes, 327
 with stridor, 328
- Urate crystals, 211, 211
- Urea breath tests, 47, 47
- Ureidopenicillin, 377
- Ureteric colic *see* Renal/ureteric colic
- Urgency, defined, 260–261
- Urinary tract disease, presentation, 223
- Urinary tract infection (UTI), 5, 7, 179–181, 260–262
 case history, 179–180, 260
 examination, 180, 261–262
 history taking, 180–181
 investigations, 180, 261
 management, 261–262
 treatment, 181
- Urine output, 230–233
 case history, 230
 history taking/examination, 231–233
 management, 231, 232
 poor, causes, 231, 231
- Urine tests, 245
- Urticaria (hives), 545–548, 545
 classification, 546
 management, 546–547, 552
- UVA wavelengths, 549
- UVB wavelengths, 549
- V**
- Valaciclovir, 17
- VALIANT trial, 302
- Valsartan, 301–302, 327
- Valvular heart disease, 306–309
 prosthetic valves problems, 309
 pulse patterns, 307
 surgery, 308
see also Mitral valve disease
- Vancomycin, 6, 378
- Varicella zoster virus *see* Shingles
- Vascular disease, 254–255

- Vasculitis, 542
 haemoptysis, 334
 inflammatory autoimmune, 251–253
 leg ulcers, 542–543
 multisystem, 251–253
 treatment, 258
see also Systemic lupus disease/
 vasculitis
- Vasovagal attacks, 497
- Vasovagal syncope, 265
- Vaughan-Williams classification, arrhythmias, 273
- Venesect, 349
- Venlafaxine, 160
- Venous hypertension, 542
- Venous thromboembolic disease (VTE), 118–119
 warfarin and, 118–119, 119
- Venous ulcers, 543
- Ventilator-associated pneumonia, 350
- Ventricular ‘escape’ rhythms, 300
- Ventricular tachycardia (VT), 270–272, 272, 300
 adenosine, 274
 features, 271–272, 271
 management, 274
- Venturi mask, 343
- Verapamil, 274, 277
- Verotoxin-producing *E. coli* (VTEC) *see* *Enterohaemorrhagic Escherichia coli* (EHEC)
- Vertigo, 469–474
 case history, 469
 causes, 471
 diagnosis, 470–472
see also Benign paroxysmal positional vertigo (BPPV)
- Vestibular neuronitis, 470
- Vicia faba* (fava beans), 103
- Vinca alkaloids, 515
- Violent patients, 531–532
- Viral infections, 146–147
- Viral meningitis, 494
- Viral (de Quervain’s) thyroiditis
 case history, 437
 diagnosis, 437
 features, 437–438
- Viridans streptococci, 310
- Vision, loss of, 466–467
 case history, 466–467
 diagnosis, 466–467
 differential diagnosis, 466–467, 466
- Visual hallucinations/illusions, 509
- Vitamin B, 71
- Vitamin B₁₂ deficiency, 81, 81, 83
- Vitamin C, 71
- Vitamin D, 213
- Vitamin E, 158
- Vitamin K, 102, 102, 112
- Vitamin K deficiency, 108
 causes, 108
 management, 109
- Vomiting, 31–43
 case history, 31
 causes, 31
 investigations, 32, 32, 33
see also Haematemesis/
 melaena

W

- Walking difficulty, 499–501
 case history, 499–500
 diagnosis, 500–501, 500
- Warfarin, 323, 433
 anti-phospholipid syndrome, 209
 bleeding disorders, 111–112
 pleural effusion, 368
 thrombosis, 117
 transient ischaemic attack (TIA), 175, 476
 venous thromboembolic disease (VTE), 118–119, 119
- Waterlow Score, pressure ulcers, 163, 165, 179
- Wegener’s granulomatosis, 251–253
- Weight loss, 34–35
 case history, 34
 diagnosis, 34
 investigations, 34–35, 35
- Wernicke-Korsakoff syndrome, 71, 521
- White blood cell count, elevated, 97–98
 case history, 97
 causes, 97, 97
 investigations, 97–98

Wolff–Chaikoff effect, [439](#), [440](#)
Wolff–Parkinson–White (WPW)
 tachycardia, [270](#)
World Health Organization
 (WHO), [15](#), [216](#)
WOSCOPS trial, [302](#)

X

Xanthochromia, [501](#)
Xerosis, [563–564](#)

Z

Zolmitriptan, [467](#)

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