- The author's study[9] identified alcohol dependence in 9.7% of the population studied and a further group of problem drinkers that included the 'explosive' or binge drinker (see FIG. 12.2). Problem drinkers represent about 15–20% of the population.

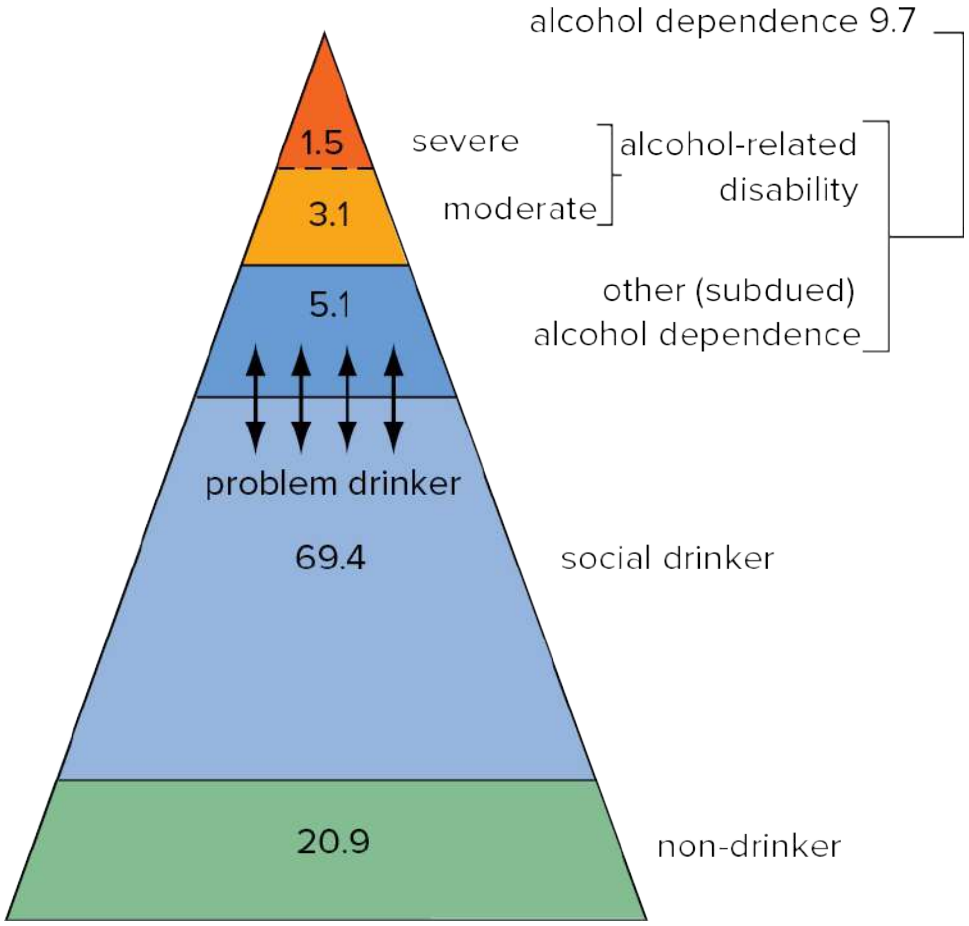

FIGURE 12.2 Prevalence of alcohol drinking patterns in the adult population (figures expressed as a percentage)

National Health and Medical Research Council (NHMRC) revised guidelines addressing harmful drinking are presented in TABLE 12.2 .[10,11]

Table 12.2 Recommended guidelines to reduce health risks from drinking alcohol, NHMRC 2020[10]

Guideline 1 Reducing the risk of alcohol-related harm over a lifetime For healthy men and women, drinking no more than 10 standard drinks a week reduces the lifetime risk of harm from alcohol-related disease or injury.
Guideline 2 Reducing the risk of injury on a single occasion of drinking

Healthy men and women should drink no more than 4 standard drinks on a single occasion, and then should not drink at all for 2–3 days.

Guideline 3 Children and young people under 18 years of age should not drink alcohol

Guideline 4 Maternal alcohol consumption can harm the developing fetus or breastfeeding baby

a. Women who are pregnant or planning a pregnancy should not drink alcohol.
b. For women who are breastfeeding not drinking is safest for their baby.

High-risk and harmful drinking occurs at >6 standard drinks (SDs) a day (average) for men and >4 SDs for women.

The main causes of alcohol-related deaths are road trauma, cancer and alcoholic liver disease.[10]

Clinical pointers to alcohol abuse

Facial features of the patient can be a helpful pointer, albeit of the more advanced drinker. These include:

- plethoric facies
- puffy ‘greasy’ facies
- telangiectasia
- rosacea + rhinophyma
- suffused (‘bloodshot’) conjunctivae
- prominent lower lip with cheilitis of corners of mouth
- smell of stale alcohol or very ‘minty’ sweet breath (masking effect)

Taking a drinking history

This requires tact and skill and it must be noted that many problem drinkers considerably understate the level of their intake.

Useful strategies[9]

- Ask questions as part of a matter-of-fact enquiry into health risk factors, such as smoking and diet.
- Place the onus of denial on the patient by asking questions such as ‘When did you

last drink alcohol?’ rather than ‘Do you ever drink alcohol?’

- Record your patient’s intake quantitatively in terms of standard drinks or grams of alcohol.
- Confirm the history by enquiring about the time spent drinking per day and expenditure on alcohol.

Useful questionnaires

There are several questionnaires that can be most helpful, assuming the patient is fully cooperative. Two or more positive replies for the CAGE questionnaire[12] are suggestive of a problem drinker.

1. Have you ever felt you should CUT down on your drinking?
2. Have people ANNOYED you by criticising your drinking?
3. Have you ever felt bad or GUILTY about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (an EYE-OPENER)

Laboratory investigations

The following blood tests may be helpful in the identification of excessive chronic alcohol intake:

- blood alcohol
- serum GGT: elevated in chronic drinkers (returns to normal with cessation of intake)
- MCV: >96 fL

Other changes:

- abnormal liver function tests (other than GGT)
- carbohydrate-deficient transferrin (quite specific—dependent on an enzyme induced by alcohol)
- HDLs elevated
- LDLs lowered
- serum uric acid elevated

Measuring alcohol intake

One standard drink contains 10 g of alcohol, which is the amount in one middy (or pot) of standard beer (285 mL), two middies of low-alcohol beer or five middies of super-light beer. These are equal in alcohol content to one small glass of table wine (122 mL), one glass of sherry or port (60 mL), or one nip of spirits (30 mL) (see FIG. 12.3).

FIGURE 12.3 Standard drinks

- 1 stubbie or can of full-strength beer = 1.4 standard drinks
- 1 light beer = 0.9 standard drinks
- 1 × 750 mL bottle of beer = 2.6 standard drinks
- 1 × 750 mL bottle of wine = 7 standard drinks

Alcohol dependence

Alcohol dependence is a syndrome in which an individual demonstrates clinically significant impairment or distress as manifested by three or more of the following, occurring at any time in the same 12-month period:

1. tolerance
2. withdrawal
3. drinking in larger amounts or for a longer period than intended
4. unsuccessful attempts to cut down or control drinking
5. a great deal of time spent in activities necessary to obtain, use or recover from the effects of alcohol

6. important social, occupational or recreational activities reduced or given up because of drinking

7. continued drinking despite knowledge of having persistent or recurrent problems caused by or exacerbated by drinking

Approach to management

The challenge to the family doctor is early recognition of the problem. There are specific target areas which should be considered carefully by the GP. Several studies have shown that early intervention and brief counselling by the doctor are effective in leading to rehabilitation.[13] Some of the results are very revealing.

- Patients expect their family doctor to advise on safe drinking levels.
- They will listen and act on our advice.[14]
- Treatment is more effective if offered before dependence or chronic disease has developed.[14]

Of prime concern to the GP is the assessment of whether the patient is interested in changing his or her excessive drinking behaviour. The proposed model of change by Prochaska and DiClemente helps identify the stage reached by the patient (see FIG. 12.4).[15]

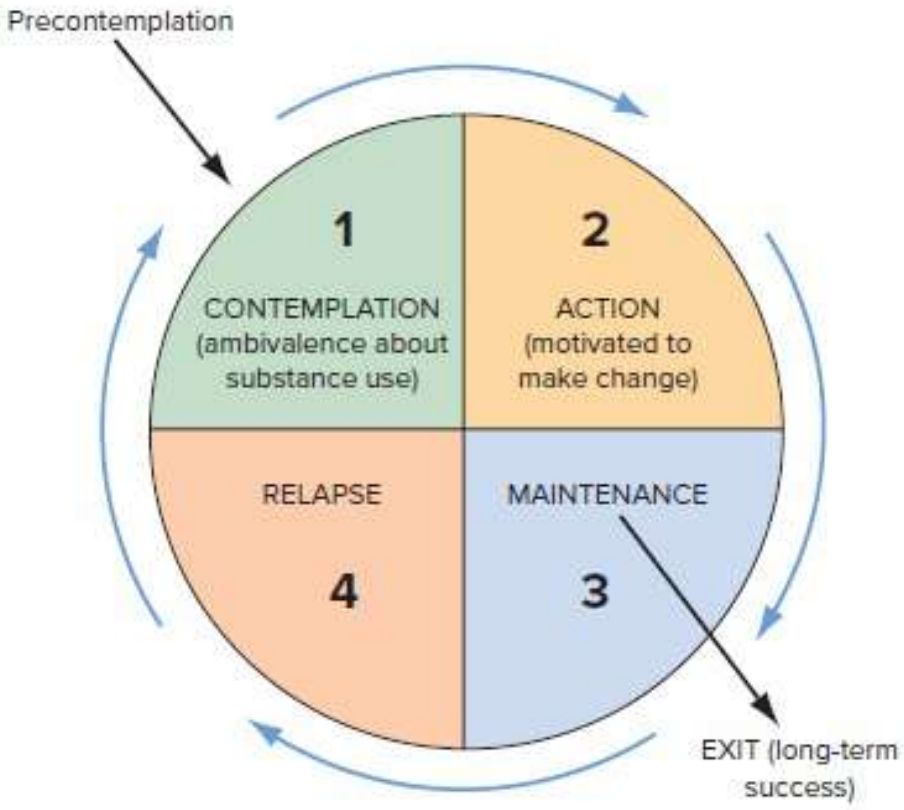

FIGURE 12.4 Prochaska and DiClemente's[15] proposed model of change to facilitate the identification of behavioural stages and the provision of counselling for treating dependence on alcohol, tobacco and other drugs

Precontemplators are satisfied users who are either unconcerned about their drinking or have no desire to change. However, if there is any evidence of ambivalence or concern about drinking, then the opportunity exists for motivational interviewing techniques.

Patients are not likely to offer concern about their drinking problem spontaneously but are often receptive to the initiative coming from their doctor.

The family doctor is ideally placed to identify and treat the problem of alcohol because the individual who abuses alcohol will tend to surface at some point in the provision of primary health care.

A brief practical management plan[16]

Giving patients feedback about their level of alcohol consumption, presenting objective evidence of harm and setting realistic goals for reducing alcohol intake induces many to change their drinking behaviour.

A six-step management plan, which has been employed in a general-practice early intervention program, is as follows:

1. Feed back the results of your assessment and specifically the degree of risk associated with their daily alcohol intake and bout drinking. Emphasise any damage that has already occurred.
2. Listen carefully to their reaction. They will need to vocalise their feelings and may respond defensively.
3. Outline the benefits of reducing drinking (e.g. save money, better health, weight loss).
4. Set goals for alcohol consumption that you both agree are feasible. In most cases this will involve reduction to below certain 'safe limits'.
    - For men: aim for fewer than 12 SDs per week.
    - For women: aim for fewer than 8 SDs per week. It is best for pregnant women not to drink.
    - For patients with illness who are physically dependent on alcohol, long-term abstinence is advisable.
5. Set strategies to keep below the upper safe limits, e.g.:
    - quench thirst with non-alcoholic drinks before having an alcoholic one
    - switch to low-alcohol beer
    - take care which parties you go to: avoid constant parties and other high-risk situations
    - explore new interests—fishing, cinema, social club, sporting activity
6. Evaluate progress by having patients monitor their drinking by using a diary; check that any abnormal blood test results are returning to normal. Make a definite appointment for follow-up and give appropriate literature such as *Alcohol: Harmful Use of Alcohol.* Obtain consent for a telephone follow-up. A useful minimum intervention plan is presented in TABLE 12.3 .

Table 12.3 Minimum intervention technique plan (5–10 minutes)

1. Advise reduction to safe levels
2. Outline the benefits
3. Provide a self-help pamphlet
4. Organise a diary or other feedback system
5. Obtain consent for a telephone follow-up
6. Offer additional help (e.g. referral to an alcohol and drug unit or to a support group)

Follow-up (long consultation 1 week later)

Review the patient's drinking diary. Explore any problems, summarise, listen and provide support and encouragement. If appointment is not kept, contact the patient.

Specialist services

According to progress and the patient's wishes and consent, specialist treatment units, group therapy and attendance at meetings of Al-Anon or AA are potential sources of help to keep the alcohol-dependent person abstinent and coping.

'Anti-craving' drugs

The following show a modest effect on assisting abstinence:

- acamprosate 666 mg (o) tds (if ≤60 kg)
- naltrexone 50 mg (o) daily (under close supervision)
- consider a combination of the above 2 drugs

Note: Disulfiram can be helpful in highly motivated people but its use, as for the above agents, is recommended under specialist advice.

Withdrawal symptoms

Symptoms of a 'hangover' include headache, nausea, irritability, malaise and a mild tremor. Withdrawal from alcohol in a chronic problem drinker includes:

- agitation/anxiety
- prominent tremor
- sweating
- insomnia
- seizures (occasionally)
- delirium tremens (DTs)

The aim of treatment for acute withdrawal symptoms is to prevent development of DTs. Maintain fluid, electrolytes and nutrition. Add vitamin B complex, including thiamine, because the patient is invariably thiamine deficient.

If medication is required (specialised advice):

- diazepam 20 mg (o) every 2 hours (up to 100 mg (o) daily, although 60 mg is usually adequate) titrated against clinical response (taper off after 2 days) in the hospitalised or well-supervised patient
- thiamine 100 mg IM or IV daily for three days, then 300 mg (o) daily for several weeks
- vitamin B group supplement IM daily
- for psychotic features add haloperidol 1.5–5 mg (o) bd or 5 mg IM as single dose if necessary

Alcohol withdrawal delirium (delirium tremens)

DTs is a serious life-threatening withdrawal state. It has a high mortality rate if inadequately treated and hospitalisation is always necessary.

Clinical features

- May be precipitated by intercurrent infection or trauma
- 1–5 days after withdrawal (usually 3–4 days)
- Disorientation, agitation
- Clouding of consciousness
- Marked tremor
- Visual hallucinations (e.g. spiders, pink elephants)
- Sweating, tachycardia, pyrexia
- Signs of dehydration

Treatment

- Hospitalisation with alcohol specialist advisory service
- Correct fluid and electrolyte imbalance with IV therapy
- Treat any systemic infection
- Thiamine (vitamin B1) 300 mg IM or IV daily for 3–5 days, then thiamine 300 mg (o) daily
- Diazepam 20 mg (o) every 2 hours (up to max. 100 mg daily) until symptoms subside. This dose is usually required for 2–3 days, then should be gradually reduced until finished. If psychotic features (e.g. hallucinations and delusions), add haloperidol 0.5–2 mg (o) bd every 2 hours, titrated to clinical response (max. 10 mg/24 hours).

Note: Chlorpromazine is not recommended because of its potential to lower seizure threshold. Diazepam and haloperidol may worsen the symptoms of hepatic toxicity.

Alcohol overdose

Overdose is potentially fatal. The average lethal blood alcohol concentration is about 0.45–0.5%. Death from a lower concentration may occur with other sedative drugs. Alcohol withdrawal may begin at 0.1%. Treatment of overdose is supportive and symptomatic. No stimulants should be given. Overdose may cause hypoglycaemia and metabolic acidosis.

Hangover

A type of acute drug toxicity causing headache, nausea and fatigue.

Prevention

- Drink alcohol on a full stomach.
- Select alcoholic drinks that suit you: avoid champagne.
- Avoid fast drinking—keep it slow.
- Restrict the quantity of alcohol.
- Dilute your drinks.
- Avoid or restrict smoking while drinking.
- Drink three large glasses of water before retiring.

Treatment

- Drink ample fluids especially water because of relative dehydration effect of alcohol.
- Take two paracetamol tablets for headache.

- Drink orange juice or tomato juice, with added sugar.
- A drink of honey in lemon juice helps.
- Tea is a suitable beverage.
- Have a substantial meal but avoid fatty food.

Illicit drugs

Several psychotropic substances are used for their effects on mood and other mental functions. Many of the severe problems are due to withdrawal of the drug. Symptomatic behaviour common to illicit drugs includes:

- rapid disappearance of clothing and personal belongings from home
- signs of unusual activity around hang-outs and other buildings
- loitering in hallways or in areas frequented by addicts
- spending unusual amounts of time in locked bathrooms
- inability to hold a job or stay in school
- rejection of old friends
- using the jargon of addicts

Illicit substance abuse

The drugs described below and in TABLES 12.4 and 12.5 are all commonly abused. Cannabis was the most widely used illicit drug in Australia in 2019, and was more frequently used than other illicit drugs.

Cocaine use increased from 2.5% in 2016 to 4.2% in 2019.[17] This includes crack, which is a cocaine base where the hydrochloride has mostly been removed, usually in a microwave oven. Crack can be inhaled or smoked (see FIGS 12.5 and 12.6). However, use of ice, which is the crude form of methamphetamine, a derivative of amphetamine (FIG. 12.6), was the main form of meth/amphetamine drug use during 2019. Speed is dexamphetamine.

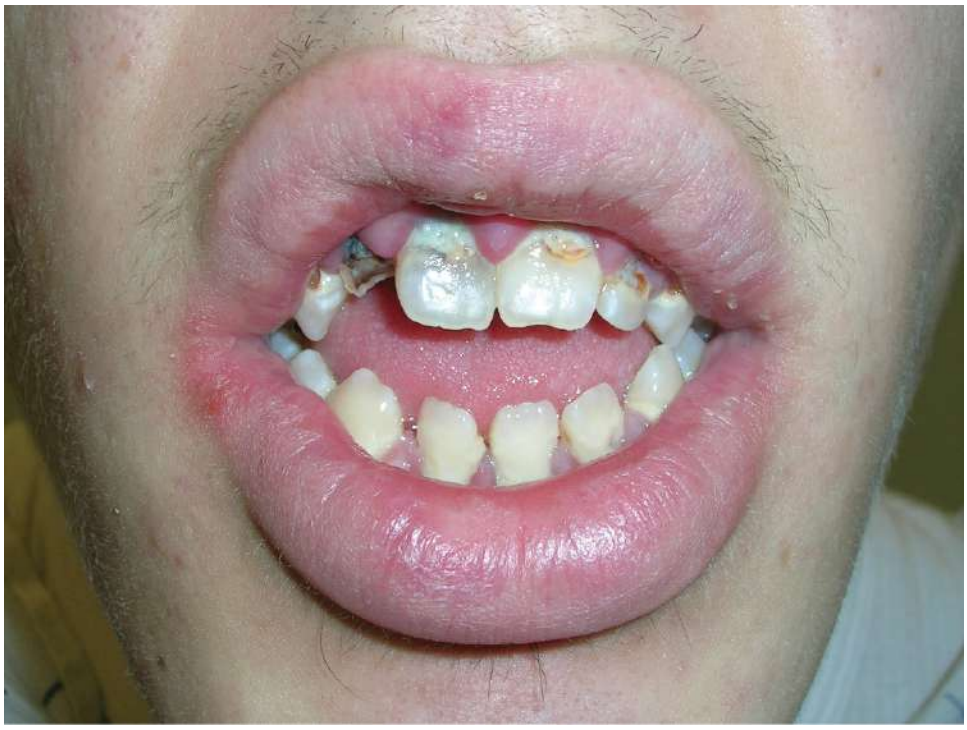

FIGURE 12.5 ‘Meth mouth’ in a young man actively smoking methamphetamine

FIGURE 12.6 Methamphetamine ice with pipe

Party drugs

Ecstasy is another ‘designer’ drug which is an amphetamine derivative—methylenedioxy-methamphetamine (MDMA). It has high abuse potential, some hallucinogenic properties and a tendency to neurotoxicity, as proved on PET brain scans. It is popular in rave parties. Deaths have occurred, reportedly in association with relative dehydration or excessive hydration. Treatment for overdosage involves correction of fluid and electrolyte disturbances. An increasingly popular drug is fantasy (gamma-hydroxybutyrate), which has sedative and anaesthetic effects similar to alcohol. A popular party drug, it is implicated as a ‘date rape’ drug. There is no specific antidote.[16] Another party drug is ketamine, which is a short-acting anaesthetic with hallucinogenic properties. It can produce nausea and vomiting if used with alcohol. Like fantasy, treatment of overdosage is symptomatic. Local anaesthetics can be dangerous in amphetamine users because of cardiotoxicity. The most common party drugs reportedly used for drink spiking are alcohol, flunitrazepam (Rohypnol), GHB (fantasy), ecstasy, LSD and ketamine.

The drug list

In 2019, 16.4% of Australians had used an illicit drug in the past 12 months. The most commonly used drugs were:[18]

- cannabis 11.6%
- cocaine 4.2%
- non-medical use of pharmaceuticals (including opiods, benzodiazepines) 4.2%
- ecstasy 3%
- hallucinogens 1.6%
- inhalants 1.4%
- meth/amphetamine 1.3%
- ketamine 0.9%
- injected drugs 0.3%

Source: National Drug Strategy Household Survey 2019

A summary of the effects of illicit or hard street drugs is presented in TABLE 12.4 .

Table 12.4 Illicit substance abuse: a summary of hallmarks

Drug	Physical symptoms	Look for	Dangers
Amphetamines including methamphetamines (3 forms) • speed—powder • base—oily paste • ice—crystalline	Aggressive or agitated behaviour; giggling; silliness; euphoria; rapid speech; fever; confused thinking; anorexia; insomnia; extreme fatigue; dry mouth; shakiness; anxiety	Jars of pills of varying colours; chain smoking; white powder and crystals can also be snorted or injected	Hypertension; death from overdose; hallucinations; paranoia; may cause temporary psychosis; stroke; cardiac arrest
Ecstasy (methylene-dioxymethamphetamine)	Anxiety; panic; sweating; 'loving' feelings; jaw clenching, teeth grinding; bizarre overactive behaviour; hallucinations; increased heart rate, BP and body temperature; confidence; feelings of happiness and love	Small tablets of various colours, shapes, sizes and designs; also comes in powder and capsules	Convulsions; risk of death from heart attack, cerebral haemorrhage, hyperthermia, fluid imbalance with hyponatraemia, acute kidney failure, DIC, liver toxicity; hangover; depression
Fantasy (gamma-hydroxybutyrate)	Relaxation and drowsiness; dizziness; relaxed inhibition/euphoria; increased sexual arousal; impaired mobility and speech	Colourless, odourless liquid; also powder and capsules	Tremors and shaking; amnesia; coma; convulsions; death from high doses
Barbiturates	Drowsiness; stupor; dullness; slurred speech; drunk appearance; vomiting	Pills of various colours	Death from overdose or as a result of withdrawal; addiction; convulsions
Cannabis/marijuana	Initial euphoria; floating feeling; sleepiness; lethargy; wandering mind;	Strong odour of burnt leaves; small seeds in pocket lining;	Inducement to take stronger narcotics; recent medical findings reveal

	enlarged pupils; lack of coordination; craving for sweets; changes of appetite; memory impairment; tacchycardia	cigarette paper; discoloured fingers	that prolonged usage causes cognitive defects, precipitates or exacerbates schizophrenia; hyperemesis
Volatile substances including glue, solvents or petrol sniffing	Aggression and violence; drunk appearance; slurred speech; dreamy or blank expression; hallucinations; ataxia	Tubes of glue; glue smears; large paper or plastic bags or handkerchiefs	Lung/brain/liver damage; death through suffocation or choking
LSD (lysergic acid diethylamide)	Severe hallucinations; feelings of detachment; incoherent speech; cold hands and feet; vomiting; laughing and crying	Cube sugar with discolouration in centre; strong body odour; small tube of liquid	Suicidal tendencies; unpredictable behaviour; chronic exposure causes brain damage; LSD causes chromosomal breakdown
Narcotics (a) opioids (e.g. heroin)	Stupor/drowsiness; marks on body; watery eyes; loss of appetite; running nose; constricted pupils; loss of sex drive; agitation; hypoventilation	Needle or hypodermic syringe; cotton; tourniquet—string, rope, belt; burnt bottle, caps or spoons; bloodstain on shirt sleeve; glass in envelopes	Death from overdose; respiratory depression; mental deterioration; destruction of brain and liver; hepatitis; embolisms
(b) cocaine	Similar effects to amphetamines—muscle pains, irritability, paranoia	Powder: in microwave ovens; inhaled, snorted or	Hallucinations; death from overdose—sudden death from

	paranoia, hyperactivity, jerky movements, euphoria, dilated pupils	snorted or injected	from arrhythmias; seizures; mental disorders; severe respiratory problems

A list of street drugs and their slang names is presented in TABLE 12.5 .

Table 12.5 A street drug dictionary

Amphetamines or uppers	
Benzedrine	Roses, beanies, peaches
Dexedrine	Dexies, speed, hearts, pep pills, fast, go-ee, uppers, sulphate
Methamphetamines	Meth, crystals, white light, ice, whiz
Drinamyl	Purple hearts, goof balls
Amphetamine derivatives	
Ecstasy	E, eggs, eckies, XTC, ‘the love drug’, Mitsubishis, MDMA, vitamin E, X, Adam, death
Crank	Crystal M, crank
Hallucinogens	
LSD	Acid, blue cheer, strawberry fields, barrels, sunshine, pentagons, purple haze, peace pills, blue light, trips
Cannabis (Indian hemp)	Hash, resin
1 Hashish (the resin)	Pot, tea, grass, hay, weed, locoweed, Mary Jane, rope, bong, jive, Acapulco gold
2 Marijuana (from leaves)	Reefers, sticks, muggles, joints, spliffies, head, smoko, ganga
Cigarettes	Blow a stick, blast a joint, blow, get high, get stoned
Smoking pot	

Narcotics	
Morphine	Morph, Miss Emma
Heroin	H, Big H, Big Harry, GOM (God's own medicine), crap, junk, horse dynamite (high-grade heroin), lemonade (low-grade heroin). Injection of dissolved powder: mainlining, blast, smack. Inhalation of powder: sniffing
Cocaine	Coke, snow, lady of the streets, nose candy, ICE, snort, C, flake, rock, blow, vitamin C, crack, shabu, baby
H & C	Speed balls
Oxycontin	Hillbilly heroin
Miscellaneous	
Fantasy	GBH (grievous bodily harm), liquid G, liquid E, liquid ecstasy, liquid X, fantasy
Barbiturates	Devils, barbies, goof balls
Benzodiazepines	Rowies, moggies
Ketamine	'K', vitamin K, special K, K hole
Solvents	Chroming

Opioid (narcotic) dependence

This section will focus on heroin dependence, although opioids such as codeine and controlled dose agents such as oxycodone and morphine are problematic.

Page 119

Typical profile of a heroin-dependent person[19]

Page 120

- Male or female: 16–30 years
- Family history: often severely disrupted, such as parental problems, early death, separation, divorce, alcohol or drug abuse, sexual abuse, mental illness, lack of affection
- Personal history: low threshold for toleration, unpleasant emotions, poor academic record, failure to fulfil aims, poor self-esteem
- First experiments with drugs are out of curiosity, and then regular use follows with loss of job, alienation from family, finally moving into a 'drug scene' type of lifestyle

Methods of intake

1. Oral ingestion
2. Inhalation (see FIG. 12.5)
   - intranasal
   - smoking
3. Parenteral
   - subcutaneous
   - intramuscular
   - intravenous (see FIG. 12.7)

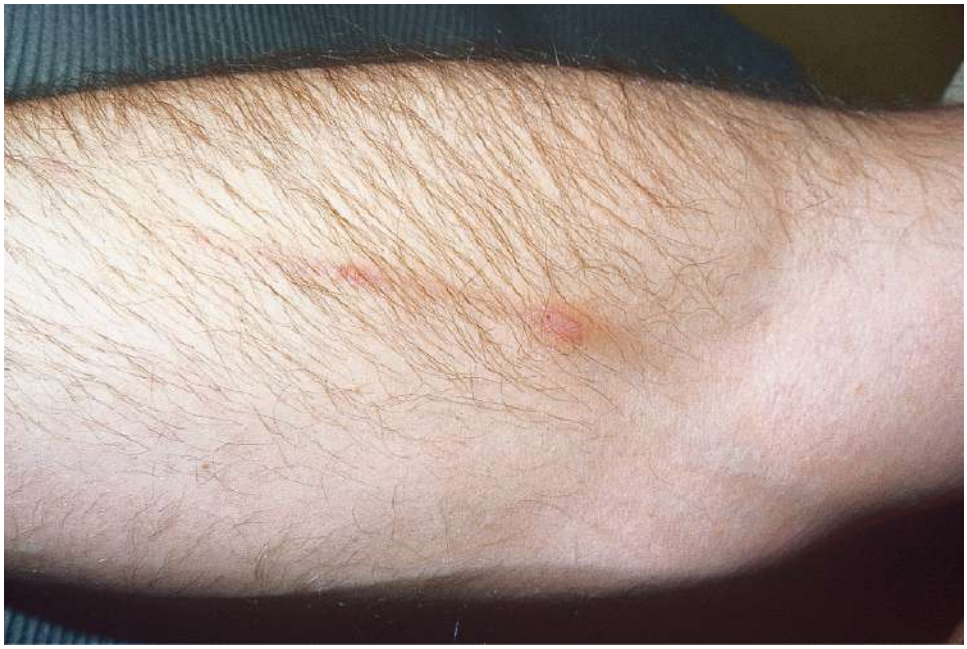

FIGURE 12.7 Intravenous heroin injection signs: linear tracks and scarring from repeated venepunctures along the course of a vein. Less common sites are the lower leg, dorsum of foot, neck and dorsal vein of penis.

Photo courtesy John Jagoda

Opioid withdrawal effects[19,20]

These develop within 12 hours of ceasing regular usage. Maximum withdrawal symptoms usually occur between 36 and 72 hours and tend to subside after 10 days.

- Anxiety and panic
- Irritability
- Chills and shivering
- Excessive sweating
- ‘Gooseflesh’ (cold turkey)
- Loss of appetite, nausea (possibly vomiting)
- Lacrimation/rhinorrhoea
- Tiredness/insomnia
- Muscle aches and cramps
- Abdominal colic
- Diarrhoea

A secondary abstinence syndrome is identified[19] at 2–3 months and includes irritability, depression and insomnia.

Complications of opioid dependence

Medical

- Overdose reaction: agitation, respiratory depression—may include fatal cardiopulmonary collapse. Since the early 2000s opioid deaths have fallen from peak levels of the 1990s, when there was a glut of heroin.
- Injection site: scarring, pigmentation, thrombosis, abscesses, ulceration (especially with barbiturates)
- Distal septic complications: septicaemia, infective endocarditis, lung abscess, osteomyelitis, ophthalmitis
- Viral infections: hepatitis B, hepatitis C (refer to CHAPTER 47), HIV infection (refer to CHAPTER 18)
- Neurological complications: transverse myelitis, nerve trauma
- Physical disability: malnutrition

Social

- Alienation from family, loss of employment, loss of assets, criminal activity (theft, burglary, prostitution, drug trafficking)

Management

Management is complex because it includes the medical management not only of physical dependence and withdrawal but also of the individual complex social and emotional factors. The issues of impaired liver function, hepatitis B and C and HIV prevention also have to be addressed. Sociological tests for these illnesses should be considered.

Patients should be referred to a treatment clinic and then a shared-care approach can be used. The treatments include cold turkey (abrupt cessation) with pharmacological support, acupuncture, high doses of vitamin C, methadone substitution and drug-free community education programs.

Maintenance programs that include counselling techniques are widely used for heroin dependence. Acute toxicity requires injections of naloxone.

Opioid withdrawal[20]

Buprenorphine controlled withdrawal (short term) is used to prevent the emergence of a withdrawal syndrome in contradistinction from buprenorphine maintenance, where there is an extended treatment period.

Initial dose

- buprenorphine 4–8 mg (sublingual) as a single daily dose, increasing to 12 mg (max) on day 3, then reduce gradually over the next 3–5 days

Note: If autonomic signs, use clonidine 5–15 mg/kg/day (o) in 3 divided doses for 7–10 days then taper off. If anxiety and agitation, use diazepam 5–20 mg (o) qid (with care). Clonidine can be used as first-line treatment because of relative safety but buprenorphine is preferred to clonidine and methadone for the management of opioid withdrawal. Avoid benzodiazepines unless supervision is available.

Maintenance programs for long-term opioid dependence[20]

There are currently three alternative programs—methadone, buprenorphine and naltrexone—which are substitutes for heroin and other opioids. Seek specialist advice for the management of these drugs.

Methadone

Seek specialist advice before starting treatment. The dose needs to be determined individually according to past use and initial response to methadone.

- methadone 20 mg (o) daily initially. Stabilise dose over 3 weeks. Beware of doses >40 mg, especially in unwell patients. Maintenance 50–80 mg (o) daily. Usual maximum dose 120 mg.

Buprenorphine

- buprenorphine 2–8 mg sublingual, once daily initially, increase to 8–24 mg daily or alternative days once stabilised. It is less dependent and prone to overdose than methadone but can precipitate withdrawal if used too soon.

Naltrexone

Care is required in giving naltrexone to a person physically dependent on opioids. A naloxone challenge test is used.[20] If no evidence of withdrawal give:

- naltrexone 25 mg (o) initially, increasing to 50 mg daily on day 2 if tolerated. Careful supervision with appropriate counselling is required.

The natural history of opioid dependence indicates that many patients do grow through their period of dependence and, irrespective of treatments provided, a high percentage become rehabilitated by their mid-30s.

Stimulant substance abuse

The stimulants include amphetamines and their analogues, ephedrine, designer drugs such as MDMA and ‘fantasy’, cocaine and certain appetite suppressants. The amphetamines include the common methamphetamine, dexamphetamine and the original amphetamines. Another disturbing drug is the stimulant ‘monkey dust’, a synthetic cathinone, also known as ‘bath salts’ or MDPV. It is similar to the amphetamine designer drug ‘meow-meow’ (mephedrone). These agents can induce a psychosis with dangerous behaviour including irrational risk taking and violent behaviour.

Stimulant-induced syndrome[20]

- Aggressive behaviour
- Paranoid behaviour
- Irritability
- Transient toxic psychosis
- Delirium
- Schizophrenic-like syndrome
- Increased sexual behaviour

Treatment

- Withdrawal of drugs

- Cognitive behaviour therapy
- Handle person carefully and respectfully
- No firm evidence on effectiveness of drugs

Stimulant-withdrawal syndrome[20]

This syndrome should be suspected in people whose occupation involves shift work, interstate transport driving or multiple jobs presenting with the following symptoms:

- drowsiness
- hypersomnia, then insomnia
- irritability
- hyperphagia
- aggressive behaviour
- depression/dysphoria; may last months
- urge to resume drugs

Treatment

- Psychological support and encouragement, e.g. CBT
- Desipramine (or similar tricyclic antidepressant) 75 mg (o) nocte (increasing as necessary)
- Bromocriptine 1.25 mg (o) bd has also been used for cocaine withdrawal

Hallucinogen abuse

Hallucinogens in use include lysergic acid diethylamide (LSD), phencyclidine (angel dust), the tropical plant products (Kava and Betel nuts) and many synthetics. Symptoms include psychotic behaviour, including severe hallucinations. Withdrawal from these drugs is not usually a problem but ‘flashbacks’ can occur. Treatment, especially where there is fear or anxiety, is diazepam 10–20 mg (o) statim.

Treatment (medication to counter symptoms)[14]

- haloperidol 2.5–10 mg (o) daily

  or

- diazepam 10–20 mg (o) repeated every 2 hours prn (to max. 120 mg daily)

Cannabis (marijuana) use

Cannabis is a drug that comes from the plant *Cannabis sativa*, the Indian hemp plant. It is a stimulant and a hallucinogen. It contains the chemical tetrahydrocannabinol, which makes people get 'high'. It is commonly called marijuana, grass, pot, dope, hash or hashish. Other slang terms are Acapulco gold, ganga, herb, J, jay, hay, joint, reefer, weed, locoweed, smoke, tea, stick, Mary Jane, Panama red and spliffy (see TABLE 12.5). Marijuana comes from the leaves, while hashish is the concentrated form of the resinous substances from the head of the female plant and can be very strong (it comes as a resin or oil). The drug is usually smoked as a leaf (marijuana) or a powder (hashish), or hashish oil is added to a cigarette and then smoked. The effects of taking cannabis depend on how much is taken, how it is taken, how often, whether it is used with other drugs and on the particular person.[21] The effects vary from person to person. The effects of a small-to-moderate amount include:

- feeling of well-being and relaxation
- decreased inhibitions
- woozy, floating feeling
- lethargy and sleepiness
- talkativeness and laughing a lot
- red nose, gritty eyes and dry mouth
- unusual perception of sounds and colour
- nausea and dizziness
- loss of concentration, slight cognitive impairment
- looking 'spaced out' or drunk
- lack of coordination
- delusions and hallucinations (more likely with larger doses)
- a form called skunk or mad weed causes paranoia

The effects of smoking marijuana take up to 20 minutes to appear and usually last 2 to 3 hours and then drowsiness follows.[21] The effect on psychomotor function is similar to alcohol and this can impair driving skills. The main problem is habitual use with the development of dependence; dependence (addiction) is worse than originally believed.

Long-term use and addiction

The influence of pot has a severe effect on the personality and drive of the users. They lose their energy, initiative and enterprise. They become bored, inert, apathetic and careless. A serious effect of smoking pot is the inability to concentrate and loss of memory. Some serious problems include:

- deterioration of academic or job performance
- anxiety and paranoia
- respiratory disease (more potent than tobacco for lung disease): causes COPD, laryngitis and rhinitis
- often prelude to taking illicit drugs
- becoming psychotic (resembling schizophrenia): the drug appears to unmask an underlying psychosis[21]
- impaired ability to drive a car and operate machinery

Withdrawal

Sudden withdrawal produces insomnia, night sweats, nausea, depression, myalgia, irritability and maybe anger and aggression. However, the effects are often mild with recovery within a few days in many, but heavy users have a severe withdrawal.

Management

No specific pharmacological treatment is available. CBT is advisable.

The best treatment is prevention. People should either not use it or limit it to experimentation. If it is used, people should be prepared to sleep it off and not drive.

Anabolic steroid misuse

The apparent positive effects of anabolic steroids include gains in muscular strength (in conjunction with diet and exercise) and quicker healing of muscle injuries. However, the adverse effects, which are dependent on the dose and duration, are numerous.

Adverse effects in women are:

- masculinisation—male-pattern beard growth
- suppression of ovarian function
- changes in mood and libido

- hair loss

In adult men, adverse effects are:

- feminisation: enlarged breasts, high-pitched voice
- acne
- testicular atrophy and azoospermia
- libido changes
- hair loss

Severe effects with prolonged use include:

- liver function abnormalities, including hepatoma
- tumours of kidneys, prostate
- heart disease

In prepubescent children there can be premature epiphyseal closure with short stature.

Drugs in sport[22]

It is important for GPs to have a basic understanding of drugs that are banned and those that are permissible for elite sporting use. The guidelines formulated by the International Olympic Committee (IOC) Medical Commission and the World Anti-Doping Agency (WADA) are generally adopted by most major sporting organisations.[13] TABLES 12.6 and 12.7 provide useful guidelines. The IOC's list of prohibited drugs is regularly revised. Banned drug groups include stimulants, narcotics, cannabinoids (e.g. marijuana), anti-oestrogen agents (e.g. tamoxifen), glucocorticosteroids (e.g. prednisolone), anabolic agents, diuretics and various hormones. Banned methods include blood doping (the administration of blood, red blood cells and related blood products), enhancement of oxygen transfer (e.g. erythropoietin, efaproxiral), gene doping and pharmaceutical, chemical and physical manipulation (substances or methods that alter the integrity and validity of the urine testing).

Table 12.6 Prohibited list: World Anti-Doping Guide (valid 1 January 2021)[22]

Classes	Examples
Prohibited substances at all times	
S1 Anabolic agents	Androstenediol, clenbuterol,

	DHEA, methandienone, methyl testosterone, nandrolone, oxandrolone, stanozolol, testosterone, tetrahydrogestrinone, tibolone, zeronol
S2 Peptide hormones, growth factors and related substances	Growth hormone, corticotrophin, chorionic gonadotrophin and LH (in males), erythropoietin (EPO), darbepoetin (dEPO), SERMS, insulin and insulin-like growth factor, ACTH *Note:* Masking agents such as probenecid, epitestosterone, diuretics and plasma expanders are banned.
S3 Beta-2 agonists	All oral beta-2 agonists, including both optical isomers (except inhaled salbutamol, eformoterol and salmeterol according to recommended guidelines)
S4 Hormone antagonists and metabolic modulators	Aromatase inhibitors, e.g. anastrozole, letrozole; SERMS, e.g. raloxifene, tamoxifen; other anti-oestrogenic substances, e.g. clomiphene; myostatin inhibitors; metabolic modulators —insulins
S5 Diuretics and other masking agents	Acetazolamide, frusemide, hydrochlorothiazide, triamterene, indapamide, spironolactone (and related substances)
Prohibited substances in competition	
S6 Stimulants	Amiphenazole, amphetamines, cocaine, ephedrine, ephedra, meldonium, mesocarb, terbutaline,* adrenaline, salmeterol,* salbutamol,* selegiline, pseudoephedrine, phenylpropanolamine,

	modafinil, phentermine
S7 Narcotics**	Diamorphine (heroin), methadone, morphine, pethidine, pentazocine, buprenorphine, hydromorphone, oxycodone, oxymorphone, fentanyl
S8 Cannabinoids	Natural (e.g. cannabis, hashish, marijuana) or synthetic THC and cannabimimetics (e.g. 'spice')
S9 Glucocorticosteroids	All glucocorticosteroids are prohibited when administered by oral, IV, IM or rectal routes
Substances prohibited in particular sports	
P1 Beta blockers	Prohibited in competition only, e.g. atenolol, carvedilol, metoprolol, propranolol, timolol (Check list and sports, e.g. archery, shooting, golf, skiing)
Prohibited methods	
Ml Manipulation of blood and blood components (blood doping, haemoglobin oxygen carriers)	
M2 Chemical and physical manipulation	
M3 Gene and cell doping	

*Permitted by inhaler but only with therapeutic use exemption (TUE).
**Caffeine, codeine, dextromethorphan, dextropropoxyphene, dihydrocodeine, tramadol, diphenoxylate and pholcodeine are permitted.
These lists are constantly being updated, so see www.wada-ama.org (World Anti-Doping Agency) or https://sportintegrity.gov.au for current information.

Table 12.7 Guidelines for treatment of specific conditions: International Olympic Committee Medical Code 2008

Asthma	
Allowed	Salbutamol inhaler, salmeterol inhaler, terbutaline inhaler, formoterol inhaler
Banned	Sympathomimetic products (e.g. ephedrine, pseudoephedrine, isoprenaline, systemic beta-2 agonists), oral corticosteroids
Cough	

Allowed	All antibiotics, steam and menthol inhalations, cough mixtures containing antihistamines, pholcodine, dextromethorphan, dihydrocodeine
Banned	Sympathomimetic products (e.g. ephedrine, phenylpropanolamine)
Diarrhoea	
Allowed	Diphenoxylate, loperamide, products containing electrolytes (e.g. Gastrolyte)
Banned	Products containing opioids (e.g. morphine)
Hayfever	
Allowed	Antihistamines, nasal sprays containing a corticosteroid or antihistamine, sodium cromoglycate preparations
Banned	Products containing ephedrine, pseudoephedrine
Pain	
Allowed	Aspirin, codeine, dihydrocodeine, ibuprofen, paracetamol, tramadol, all NSAIDs, dextropropoxyphene
Banned	Products containing opioids (e.g. morphine) or caffeine
Vomiting	
Allowed	Domperidone, metoclopramide

Restricted drugs include alcohol, marijuana, local anaesthetics, corticosteroids and beta blockers. Practitioners can check the guidelines and provide written notification to the relevant authority. Be cautious of anorectics and weight-reducing agents.

Other drug groups permitted by WADA:

- antidepressants
- antihypertensives (excluding beta blockers)
- caffeine
- eye medications
- oral contraceptives
- skin creams and ointments
- sleeping tablets

Check websites including: www.olympic.org.

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Alcohol: harmful use of alcohol
- Amphetamines
- Cocaine
- Ecstasy
- Heroin
- Smoking: quitting
- Cannabis (marijuana)

Resources

- Global DRO, Athletes, check your medications! (country-specific): www.globaldro.com; also see Sport Integrity Australia (superseded ASADA): https://www.sportintegrity.gov.au/
- Department of Health, National drug campaign: www.campaigns.health.gov.au/drughelp
- www.usada.org/substances/prohibited-list

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13 Anaemia

There's never none of these demure boys come to any proof; for thin drink doth so over cool their blood, and making many fish-meals, that they fall into a kind of male green-sickness.

WILLIAM SHAKESPEARE (1564–1616), *KING HENRY IV*

Anaemia is a label, not a specific diagnosis. Anaemia is defined as a reduction in red blood cell numbers or a haemoglobin (Hb) level below the normal reference level for the age and sex of that individual.

The WHO defines anaemia as haemoglobin <130 g/L for men, <120 g/L for women and <110 g/L in pregnant women and school-aged children.

Anaemia: a masquerade

Anaemia is regarded as a masquerade because the problem can develop surreptitiously and the patient may present with many seemingly undifferentiated symptoms before the anaemia is detected. Once identified, a cause must be found.

Key facts and checkpoints

- In Australia, most people with anaemia will have iron deficiency ranging from up to 5% for children to 20% for menstruating females.[1]
- The remainder will mainly have anaemia of chronic disorders.
- The incidence of haemoglobinopathy traits, especially thalassaemia, is increasing in multicultural Western societies.
- If a patient presents with precipitation or aggravation of myocardial ischaemia, heart failure or intermittent claudication, consider the possibility of anaemia.
- The serum ferritin level, which is low in cases of iron-deficiency anaemia, is probably the best test to monitor iron-deficiency anaemia as its level reflects the

amount of stored iron.

- Normal reference values for peripheral blood are presented in TABLE 13.1 .

Table 13.1 Normal reference values for peripheral blood: adults

	Male	Female
Haemoglobin (g/L)	130–180	115–165
Red cells (× 10^{12}/L)	4.5–6	4–5.5
PCV (haematocrit)	40–53	35–47
MCV (fL)	80–100	
Platelets (× 10^9/L)	150–400	
White cell count (× 10^9/L)	4–11	
Neutrophils	2.5–7.5	
Lymphocytes	1.5–4	
Monocytes	0.2–1	
Eosinophils	<0.5	
Reticulocytes (%)	0.5–2	
ESR (mm/hour)	<20 mm	
	<35 mm if >70 years	

Source: Reproduced with permission from Dr M Gribble[2]

DxT fatigue + palpitations + exertional dyspnoea → anaemia

Clinical features

Patients with anaemia may be asymptomatic. When symptoms develop they are usually non-specific. Symptoms can include:

- tiredness/fatigue
- muscle weakness

- headache and tinnitus
- lack of concentration
- faintness/dizziness
- dyspnoea on exertion
- palpitations
- angina on effort
- intermittent claudication
- pica—usually brittle and crunchy food, e.g. ice (iron-deficiency anaemia)

Signs

Non-specific signs include pallor, tachycardia, systolic flow murmur and angular cheilosis.

If severe, signs can include ankle oedema and cardiac failure.

Specific signs include jaundice—haemolytic anaemia, and koilonychias (spoon-shaped nails)—iron-deficiency anaemia.

History

The history may indicate the nature of the problem:

- iron deficiency: inadequate diet, pregnancy, GIT loss, menorrhagia, NSAID and anticoagulant ingestion
- folate deficiency: inadequate diet especially with pregnancy and alcoholism, small bowel disease
- vitamin B12 deficiency: previous gastric surgery, ileal disease or surgery, pernicious anaemia, selective diets (e.g. vegetarian, fad)
- haemolysis: abrupt onset anaemia with mild jaundice
- possibly lead toxicity, especially in children

Classification of anaemia

The various types of anaemia are classified in terms of the red cell size—the mean corpuscular volume (MCV):

- microcytic—MCV ≤ 80 fL

- macrocytic—MCV >100 fL
- normocytic—MCV 80–100 fL

Note: Upper limit of MCV varies from 95–100 fL depending on age and laboratory.

TABLE 13.2 outlines a classification of some of the more common causes of anaemia encountered in general practice. There can be an interchange of disorders between the above groups; for example, the anaemia of chronic disorders (chronic infection, inflammation and malignancy) can occasionally be microcytic as well as normocytic; the anaemia of hypothyroidism can be macrocytic in addition to the more likely normocytic; the anaemia of bone marrow disorder or infiltration can also be occasionally macrocytic.

Table 13.2 Classification of anaemia by mean RBC volume (MCV) with selected causes

Microcytic (MCV < 80 fL) • Iron deficiency • Thalassaemia • Anaemia of chronic disease • Sideroblastic anaemia
Microcytic (MCV > 100 fL) • Vitamin B12 deficiency • Folate deficiency • Myelodysplastic disorders • Cytotoxic drugs • Liver disease/alcoholism
Normocytic (MCV 80–100 fL) • Kidney disease • Anaemia of chronic disease • Endocrine failure/hypothyroidism • Haemolysis • Aplastic anaemia

Microcytic anaemia—MCV ≤80 FL

The main causes of microcytic anaemia are iron deficiency and haemoglobulinopathy,

particularly thalassaemia. Consider lead poisoning.

Iron-deficiency anaemia[3]

Iron deficiency is the most common cause of anaemia worldwide. It is the biggest cause of microcytic anaemia, with the main differential diagnosis of microcytic anaemia being a haemoglobinopathy such as thalassaemia. However, it is caused by bleeding until proved otherwise.

An understanding of the interpretation of iron studies is important in management.

Clinical and laboratory features

- Microcytic anaemia
- Serum ferritin level low (NR: F 15–200 mcg/L: M 30–300 mcg/L)
- Serum iron level low
- Increased transferrin level
- Microcytic hypochromic red cells
- MCV ↓, MCH ↓, MCHC ↓
- Reduced transferrin saturation
- Response to iron therapy

Non-haematological effects of chronic iron deficiency

- Angular cheilosis/stomatitis
- Glossitis
- Oesophageal webs
- Atrophic gastritis
- Brittle nails and koilonychias

Causes[1]

Blood loss

- Menorrhagia
- Gastrointestinal bleeding (e.g. carcinoma, haemorrhoids, peptic ulcer, hiatus hernia, GORD,

NSAID therapy)

- Frequent blood donations
- Malignancy
- Hookworm (common in tropics)

Increased physiological requirements

- Prematurity, infant growth
- Adolescent growth
- Pregnancy

Malabsorption

- Coeliac disease
- Postgastrectomy

Dietary

- Inadequate intake
- Special diets (e.g. fad, vegetarianism)
- Pica—eating unnatural food, e.g. dirt, ashes

Investigations

Investigations are based on the history and physical examination, including the rectal examination. If GIT bleeding is suspected, the faecal occult blood test is not considered very valuable but appropriate investigations include gastroscopy and colonoscopy, small bowel biopsy and small bowel enema.

Haematological investigations: typical findings

- Microcytic, hypochromic red cells
- Anisocytosis (variation in size), poikilocytosis (shape)—pencil-shaped rods
- Low serum iron level
- Raised iron-binding capacity
- Serum ferritin level low (the most useful index)

- Soluble transferrin receptor factor—this factor is increased in iron deficiency, but not in chronic disease. Therefore, it is very helpful in differentiating iron deficiency from other forms. It is an indirect marker of what is happening in the bone marrow.[4]

The state of the iron stores is assessed by considering the serum iron, the serum ferritin and the serum transferrin levels in combination. Typically, in iron deficiency, the serum iron and ferritin levels are low and the transferrin high, but the serum iron level is also low in all infections—severe, mild and even subclinical—as well as in inflammatory states, malignancy and other chronic conditions. Serum ferritin estimations are spuriously raised in liver disease of all types, chronic inflammatory conditions and malignancy; transferrin is normally raised in pregnancy. Since each of these estimations can be altered in conditions other than iron deficiency, all three quantities have to be considered together to establish the iron status (see TABLE 13.3).[2]

Table 13.3 The interpretation of iron studies[2]

Condition	Serum Fe	TIBC	% Transferrin saturation	Ferritin
Iron deficiency	↓	N or ↑	↓	↓ ↓
β-thalassaemia	N or ↑	N	N or ↑	N or ↑
Anaemia of chronic disease	↓	N or ↓	↓	N or ↑
Sideroblastic anaemia	N or ↑	N	N or ↑	↑
Haemochromatosis	↑	↓	↑ ↑	↑ ↑

N = normal

Treatment[4,5]

- Correct the identified cause.
- Diet—iron-rich foods, vitamin C-rich foods (see TABLE 13.4). Iron is present in meat and legumes as Fe^{+++} and therefore requires gastric acid for conversion to Fe^{++}.
- Elemental iron supplements 100–200 mg daily (adults).
- Iron preparations:

  oral iron (ferrous sulphate 1–2 tablets daily between meals for 6 months), e.g. Ferro-Gradumet or Ferro-grad C (avoid taking with milk) with orange juice or ascorbic acid until Hb is normal

  parenteral iron preferably by IV infusion is probably best reserved for special

circumstances such as a failed trial of oral iron for symptomatic iron-deficiency anaemia (there is a risk of an allergic reaction, a serum sickness-like illness for 48 hours and post-infusion skin staining around the cannula site). Cover with an antihistamine or IV hydrocortisone 30 minutes beforehand. Infusion is best with ferric carboxymaltose in 0.9% (N) saline.[6] Avoid blood transfusions if possible. IM iron is not recommended.

Table 13.4 Optimal adult diet for iron deficiency

Adults should limit milk intake to 500 mL a day while on iron tablets
Avoid excess caffeine, fad diets and excess processed bread
Eat ample iron-rich foods (especially protein)
Protein foods
Meats—beef (especially), veal, pork, liver, poultry
Fish and shellfish (e.g. oysters, sardines, tuna)
Seeds (e.g. sesame, pumpkin)
Eggs, especially egg yolk
Fruits
Dried fruit (e.g. prunes, figs, raisins, currants, peaches)
Juices (e.g. prune, blackberry)
Most fresh fruit
Vegetables
Greens (e.g. spinach, silver beet, lettuce)
Dried peas and beans (e.g. kidney beans)
Pumpkin, sweet potatoes
Grains
Iron-fortified breads and dry cereals
Oatmeal cereal
For better iron absorption, add foods rich in vitamin C (e.g. citrus fruits, cantaloupe, Brussels sprouts, broccoli, cauliflower)

Response

- Anaemia responds after about 2 weeks and is usually corrected after 2 months (if underlying cause addressed).[1]
- Oral iron is continued for 3 to 6 months to replenish stores.

- Monitor progress with regular serum ferritin levels.
- A serum ferritin level >50 mcg/L generally indicates adequate stores.

Failure of iron therapy

Consider:

- poor compliance
- continuing blood loss
- malabsorption (e.g. severe coeliac disease)
- incorrect diagnosis (e.g. thalassaemia minor, chronic disease)
- bone marrow infiltration

Thalassaemia

This inherited condition is seen mainly (although not exclusively) in people from the Mediterranean basin, the Middle East, north and central India and South-East Asia, including south China. The heterozygous form is usually asymptomatic; patients show little if any anaemia and require no treatment. The condition is relatively common in people from these areas. The homozygous form is a very severe congenital anaemia needing lifelong transfusional support but is comparatively rare, even among the populations prone to thalassaemia (refer to CHAPTER 23).[2]

The key to the diagnosis of heterozygous thalassaemia minor is significant microcytosis quite out of proportion to the normal Hb or slight anaemia, and confirmed by finding a raised HbA_2 on Hb electrophoresis. DNA screening analysis is now available. The importance of recognising the condition lies in distinguishing it from iron-deficiency anaemia, for iron does not help people with thalassaemia and is theoretically contraindicated. Even more importantly, it lies in recognising the risk that, if both parents have thalassaemia minor, they run a one in four chance of having a baby with thalassaemia major in every pregnancy, with devastating consequences for both the affected child and the whole family.

Treatment of thalassaemia major is transfusion to a high normal Hb with packed cells plus desferrioxamine.

Haemoglobin E

This Hb variant is common throughout South-East Asia.[4] It has virtually no clinical effects in either the homozygous or heterozygous forms, but these people have microcytosis, which must be distinguished from iron deficiency; moreover, if the *HbE* gene is combined with the thalassaemia gene, the child may have a lifelong anaemia almost as severe as thalassaemia

major. Both genes are well established in the South-East Asian populations in Australia as well as in their own countries.

Macrocytic anaemia—MCV >100 FL

Alcohol and liver disease

Each individually, or in combination, leads to macrocytosis with or without anaemia. The importance of this finding lies in its often being the first indication of alcohol abuse, which can so frequently go unnoticed unless there is a firm index of suspicion. Chronic liver disease due to other causes may also be late in producing specific clinical symptoms.

Drug toxicity

Cytotoxic drugs, anticonvulsants in particular, and various others (see TABLE 13.5) may cause macrocytosis. This is of little clinical significance and does not need correction unless associated with anaemia or other cytopenia.

Table 13.5 Drugs causing macrocytosis[2,5]

Alcohol	
Cytotoxics/immunosuppressants	Azathioprine Methotrexate, 5-fluorouracil
Antibiotics	Cotrimoxazole, Pyrimethamine (incl. Fansidar and Maloprim) Zidovudine
Anticonvulsants	Phenytoin Primidone Phenobarbitone

Myelodysplastic syndromes

These conditions have been recognised under a variety of names, such as ‘refractory anaemia’ and ‘preleukaemia’, for a long time, but only relatively recently have they been grouped together. They are quite common in the elderly but may be seen in any age group (refer to TABLE 13.2).

These conditions frequently present as a macrocytic anaemia with normal serum vitamin B12 and red cell folate, and are unresponsive to these or any other haematinics. They are usually

associated with progressive intractable neutropenia or thrombocytopenia or both, and progress slowly but relentlessly to be eventually fatal, terminating with infection, haemorrhage or, less often, acute leukaemia.

Vitamin B12 deficiency (pernicious anaemia)

Although well recognised, this is a much less common cause of macrocytosis than the foregoing conditions. It is usually caused by lack of intrinsic factor due to autoimmune atrophic changes and by gastrectomy. Anaemia does not develop for about 3 years after total gastrectomy. Vitamin B12 deficiency may also be seen together with other deficiencies in some cases of malabsorption and Crohn disease.

Vitamin B12 (cobalamin) is found in the normal diet but only in foods of animal origin and consequently very strict vegetarians may eventually develop deficiency. Causes of food vitamin B12 deficiency are:[4]

- atrophic gastritis
- *H. pylori* infection
- H_2 receptor blockers
- PPI drugs
- other drugs, e.g. OCP, metformin
- chronic alcoholism
- HIV
- strict vegan diet

The clinical features are anaemia (macrocytic), weight loss and neurological symptoms, especially a polyneuropathy. It can precipitate subacute combined degeneration of the cord. The serum vitamin B12 is below the normal level (normal range 150–700 pmol/L).

$$\begin{aligned} \mathbf{B12} > \mathbf{220\ pmol/L} &= \mathbf{deficiency\ unlikey} \\ < \mathbf{148\ pmol/L} &= \mathbf{deficiency} \end{aligned}$$

Intrinsic factor antibody level is diagnostic.

Treatment (replacement therapy)[1]

- Vitamin B12 (1000 mcg, i.e. 1 mg) IM injection; body stores (3–5 mg) are replenished after 10–15 injections given every 2 to 3 days
- Maintenance with 1000 mcg injections every third month

- Can use crystalline oral B12
- Co-therapy with oral folate 5 mg/day (initially) is indicated.[9,10]
- Transfusion is best avoided. May need additional iron.

Folic acid deficiency

Diagnostic test: serum folate (normal range 7–45 nmol/L) and red cell folate—best test (normal >630 nmol/L).[7]

The main cause is poor intake associated with old age, poverty and malnutrition, usually associated with alcoholism. It may be seen in malabsorption and regular medication with anti-epileptic drugs such as phenytoin.[9] It is rarely, but very importantly, associated with pregnancy, when the demands of the developing fetus together with the needs of the mother outstrip the dietary intake—the so-called 'pernicious anaemia of pregnancy' which, if not recognised and treated immediately, can still be a fatal condition. Unlike vitamin B12, folic acid is not stored in the body to any significant degree and requirements have to be satisfied by the daily dietary intake, which invariably meets the requirement of 5–10 mcg/day. Folic acid is present in most fruit and vegetables, especially citrus fruits, nuts and green leafy vegetables (see CHAPTER 5).

Treatment (replacement therapy)

Oral folate 5 mg/day to replenish body stores (5–10 mg). This takes about 4 weeks but continue for 4 months. Vitamin B12 is usually given unless levels normal.

Normocytic anaemia[2] (anaemias without change in the MCV)

Acute haemorrhage

This is the most common cause of normocytic anaemia and is usually due to haematemesis and/or melaena.

Chronic disease

Chronic inflammation

Intercellular iron transport within the marrow is suppressed in inflammation so that, despite normal iron stores, the developing red cells are deprived of iron and erythropoiesis is depressed. If the inflammation is short-lived, the fall in Hb is not noticeable but, if it continues, an anaemia may develop that responds only when the inflammation subsides.

Malignancy

Anaemia may develop for the same reasons that apply to chronic inflammation.

Kidney failure

This is often associated with anaemia due to failure of erythropoietin secretion and is unresponsive to treatment, other than by alleviating the insufficiency or until erythropoietin is administered.

Haemolysis

Suspect haemolytic anaemia if there is a reticulocytosis, mild macrocytosis, reduced haptoglobin, increased bilirubin and urobilinogen. Haemolytic anaemias are relatively infrequent. The more common of the congenital ones are hereditary spherocytosis, sickle-cell anaemia and deficiencies of the red cell enzymes, pyruvate kinase and G-6-PD, although most cases of G-6-PD deficiency haemolyse only when the patient takes oxidant drugs such as sulphonamides or eats broad beans —'favism'.

Acquired haemolytic anaemias include those of the newborn due to maternal haemolytic blood group antibodies passing back through the placenta to the fetus, and adult anaemias due to drug toxicity or to acquired autoantibodies. About half of the latter are idiopathic and half associated with non-Hodgkin lymphomas, and the anaemia may be the presenting sign of lymphoma. Some of these antibodies are active only at cool temperatures—cold agglutinin disease; others act at body temperature and are the more potent cause of autoimmune haemolytic anaemia.

Keep in mind the rare acquired genetic disorder of paroxysmal nocturnal haemoglobinuria if dark morning urine is observed in the presence of anaemia. Flow cytometry is required for diagnosis.

Aplastic anaemia

This presents with clinical features of anaemia (Hb ↓), infection (WCC ↓) or bleeding (platelets ↓). Hypoplasia of bone marrow causes pancytopenia and normoctyic normochromic anaemia. Most cases are due to an autoimmune disorder; others are due to drugs and radiotherapy. Diagnosis is by bone marrow examination. Treatment includes supportive care and options such as immunotherapy, allogeneic bone marrow transplantation, stem cell transplantation and haemopoietic grow factors such as erythropoietin.[11]

Bone marrow replacement

This may be due to foreign tissue, such as carcinomatous metastases, or fibrous tissue, as in myelofibrosis; it may also be due to overgrowth by one or other normal elements of the bone marrow, as in chronic myeloid leukaemia, chronic lymphocytic leukaemia and lymphoma, as well as by acute leukaemic tissue. A leuco-erythroblastic picture, in which immature red and

white cells appear in the peripheral blood, is often seen when the marrow is replaced by foreign tissue.

Anaemia in children

Haemoglobin reference range

Infant	Term (cord blood)	135–195 g/L
	3–6 months	95–135 g/L
Child	1 year	105–135 g/L
	3–6 years	105–140 g/L
	10–12 years	115–145 g/L

Important causes of anaemia in childhood include iron-deficiency anaemia (quite common), thalassaemia major, sickle-cell anaemia and drug-induced haemolysis. Consider one of the haemoglobinopathies in children of Mediterranean, South-East Asian, Arabic or African–American descent, especially with a family history, normal ferritin level or anaemia resistant to iron therapy. Investigate with Hb electrophoresis.

Drugs that can cause haemolysis (the film will have reticulocytosis, spherocytosis and fragmented red cells) include some antibiotics (e.g. sulfamethoxazole), antimalarials and some anti-inflammatories.

Think of anaemia in adolescents, especially females with a rapid growth spurt at menarche and a relatively poor diet.

Iron deficiency in children[10]

- Iron deficiency is present in up to 10–30% of children in high-risk groups.
- It is often subclinical and anaemia develops in relatively few.
- It can lead to reduced cognitive and psychomotor performance (even without anaemia).
- High-risk groups include those infants <6 months who are premature and/or with low birthweight; toddlers 6–36 months with a diet high in cow’s milk and low in iron-containing foods; those exclusively breastfed after 6 months; those with delayed introduction of solids; those with general poor food intake; and those with lack of vitamin C in their diet. Bottle-feeding encourages a high milk intake and reduces the appetite for solid food.
- Possible clinical features include irritability, lethargy, minor behavioural changes, poor growth, dyspnoea and pallor.

Prevention

- Give iron and multivitamin supplements to very premature and low birthweight (<1000 g) infants.
- Introduce iron-containing solids early—at 4 to 5 months, e.g. cereals, vegetables, egg and meat.
- Encourage breastfeeding and avoid cow's milk in the first 12 months.[9]
- Avoid excessive cow's milk up to 24 months.
- Use iron-fortified formulas and cereals.

Important sources of iron

Infant milk formulas, meat (especially red meat, and also fish and chicken), green vegetables and legumes, dried fruit, juices, fortified cereals, egg yolk.

Treatment

Treatment is mainly with ferrous gluconate (1 mL/kg of 300 mg/5 mL mixture). Continue for 3 months after Hb has normalised.

Practice tips

- Iron-deficiency anaemia is blood-loss anaemia until proved otherwise.
- It is possible to be tired from iron deficiency without anaemia.
- Blood-loss anaemia is usually due to menorrhagia or gastrointestinal loss until proved otherwise.
- Investigations for suspected anaemia should include FBE, ESR and iron studies. Others to consider are Hb electrophoresis, vitamin B12 and folate levels, and kidney function tests.
- Hypothyroidism can cause a normocytic or a macrocytic anaemia.
- A therapeutic trial of iron (without investigations) is indefensible.
- Intramuscular injections of iron can tattoo so use with care: an IM iron dose is not 'stronger' than an oral iron dose.
- If microcytic anaemia is not responding to treatment, consider sideroblastic anaemia.

Patient education resource

Hand-out sheet from *Murtagh's Patient Education* 8th edition: Page 133

- Iron deficiency anaemia

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14 Endocrine and metabolic disorders

It would indeed be rash for a mere pathologist to venture forth on the uncharted sea of the endocrines, strewn as it is with the wrecks of shattered hypotheses, where even the most wary mariner may easily lose his way as he seeks to steer his bark amid the glandular temptations whose siren voices have proved the downfall of many who have gone before.

WILLIAM BOYD (1885–1979)

Endocrine, particularly thyroid, disorders can be a diagnostic trap in family practice and early diagnosis is a real challenge. A family practice of 2500 patients can expect one new case of thyroid disorder each year and 10 ‘cases’ in the practice.[1] Thyroid disease can be classified as thyroid dysfunction or structural, e.g. goitre. The diagnosis of an overactive or underactive thyroid can be difficult as the early clinical deviations from normality can be subtle.

The clinical diagnosis of classical Graves disease is usually obvious with the features of exophthalmos, hyperkinesis and a large goitre, but if the eye and neck signs are absent it can be misdiagnosed as an anxiety state. Elderly patients may present with only cardiovascular signs, such as atrial fibrillation and tachycardia, or with unexplained weight loss.

The hypothyroid patient can be very difficult to diagnose in the early stages, especially if the patient is being seen frequently. Hypothyroidism often has a gradual onset with general symptoms such as constipation and lethargy.

If suspected, only serum thyroid stimulating hormone (TSH) or thyrotropin should be requested initially.[2]

Other common endocrine disorders include diabetes mellitus, hyperprolactinaemia, calcium metabolic disorder, PCOS, sexual dysfunction and subclinical hypogonadism. They may be difficult to diagnose in the early stages of development. The pituitary is the master gland and its regulating hormones are depicted in FIGURE 14.1 .[3,4]

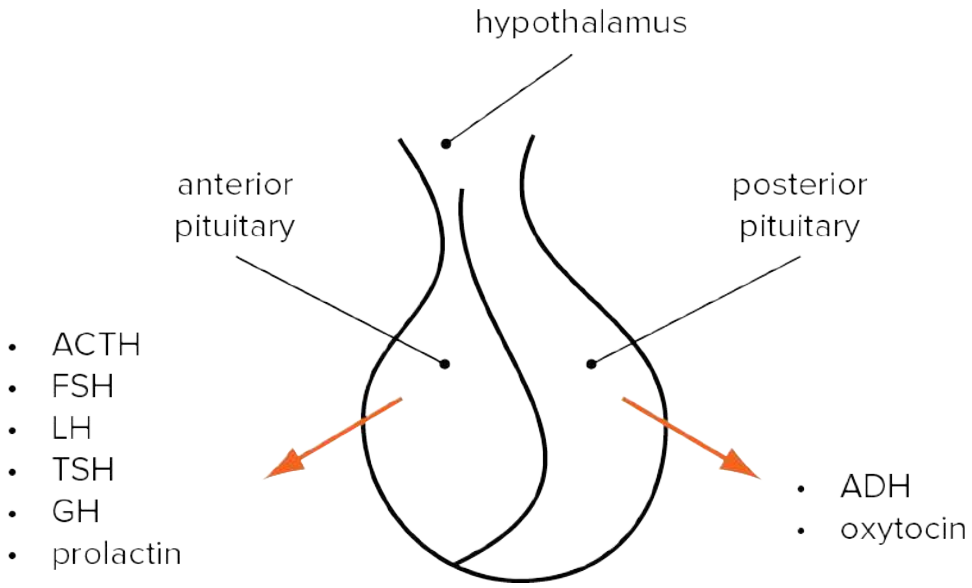

FIGURE 14.1 Pituitary hormones

Thyroid disorders

Tests for thyroid disorders[3,4]

Thyroid function tests

Advances in technology have allowed the biochemical assessment of thyroid function to change dramatically in recent years with the introduction of the serum free thyroxine (T_4) and the monoclonal TSH assays. With the highly sensitive TSH assays it is now possible to distinguish suppressed TSH levels (as in hyperthyroidism) from low and normal levels of TSH. However, the new assays are not foolproof and require interpretation in the context of the clinical picture. The serum TSH level is the most sensitive index of thyroid function and is the preferred test for suspected thyroid dysfunction. If necessary, repeat TSH in 3–6 months.

Serum free tri-iodothyronine (T_3) measurement and serum free thyroxine (T_4) can be useful in suspected T_3 toxicosis where serum T_4 level may be normal, and for monitoring patients with treated thyroid dysfunction.

The relative values are summarised in TABLE 14.1 .

Table 14.1 Summary of thyroid function tests[3]

	TSH	free T_4	free T_3	Antithyroid antibodies
Normal range	0.4–4 mU/L	10–25 pmol/L	2.6–6.0 pmol/L	
Hypothyroidism				
Primary (overt)	↑*	↓*	N or ↓ (not useful)	N or ↑
Subclinical	↑	N	N	N
Secondary (pituitary dysfunction)	N or ↓	↓	N or ↓ (not useful)	N
Hyperthyroidism (overt)	↓*	↑*	↑*	N or ↑
Subclinical	↓	N	N	N
Sick euthyroid	N or ↓	N or ↓	N or ↓	N

Notes: Results similar to hyperthyroidism can occur with acute psychiatric illness.
Normal ranges vary between laboratories.
*Main tests

Thyroid autoantibodies

Positive autoantibodies are specific for the following:[2]

- TSH receptor antibodies (TR Ab): Graves disease
- Thyroid peroxidase antibodies (TPO Ab): Hashimoto disease
- Thyroglobulin antibody (Tg Ab): Hashimoto disease

Fine-needle aspiration

This is the single most cost-effective investigation in the diagnosis of thyroid nodules. It is the best way to assess a nodule for malignancy. Care needs to be taken in the interpretation of the cytology results in conjunction with an experienced cytologist/pathologist.

Thyroid nuclear scan and imaging

The scan may help in the differential diagnosis of thyroid nodules and in causes of hyperthyroidism. A functioning nodule is said to be less likely to be malignant than a non-functioning nodule (cyst, colloid nodule, haemorrhage are non-functioning; carcinoma is usually non-functioning).

Thyroid ultrasound

A thyroid ultrasound is usually more sensitive in the detection of thyroid nodules. A

multinodular goitre may be diagnosed on ultrasound while the clinical impression may be that of a solitary nodule (the other nodules not being palpable clinically). A multinodular goitre is said to be less likely to be malignant than a solitary thyroid nodule. An ultrasound allows for follow-up of thyroid nodule(s) to note if there are any changes in size over a period of time and to then discuss appropriate intervention with the patient. It can also differentiate a solid from a cystic mass.

CT scan

CT scan of the thyroid may be used particularly to determine if there is significant compression in the neck from a large multinodular goitre with retrosternal extension. Again, follow-up CT scans may allow one to determine the progression or otherwise of such a goitre.

Hypothyroidism (myxoedema)

Primary hypothyroidism, which is relatively common, is more prevalent in elderly women (up to 5%).[5] The term *myxoedema* refers to the accumulation of mucopolysaccharide in subcutaneous tissues. The early changes are subtle and can be misdiagnosed, especially if only a single symptom is dominant.

Transient causes include subacute thyroiditis, postpartum thyroiditis and silent thyroiditis.

Common causes of primary hypothyroidism include radioactive iodine treatment, thyroid surgery and Hashimoto thyroiditis.

Patients at risk include those with:

- previous Graves disease
- autoimmune disorders (e.g. autoimmune lymphocytic thyroiditis, rheumatoid arthritis, type 1 diabetes)
- Down syndrome
- Turner syndrome
- drug treatment: lithium, amiodarone, interferon, iodine
- previous thyroid or neck surgery
- previous radioactive iodine treatment of the thyroid

Clinical features

The main features are:

- constipation

- cold intolerance
- tiredness/lethargy/somnolence
- physical slowing
- mental slowing
- depression
- huskiness of voice
- puffiness of face and eyes
- pallor
- loss of hair
- weight gain

DxT tiredness + husky voice + cold intolerance → myxoedema

Physical examination

See FIGURE 14.2 . The main signs are:

- sinus bradycardia
- delayed reflexes (normal muscular contraction, slow relaxation)
- coarse, dry and brittle hair
- thinning of outer third of eyebrows
- dry, cool skin
- skin pallor or yellowing
- obesity
- goitre

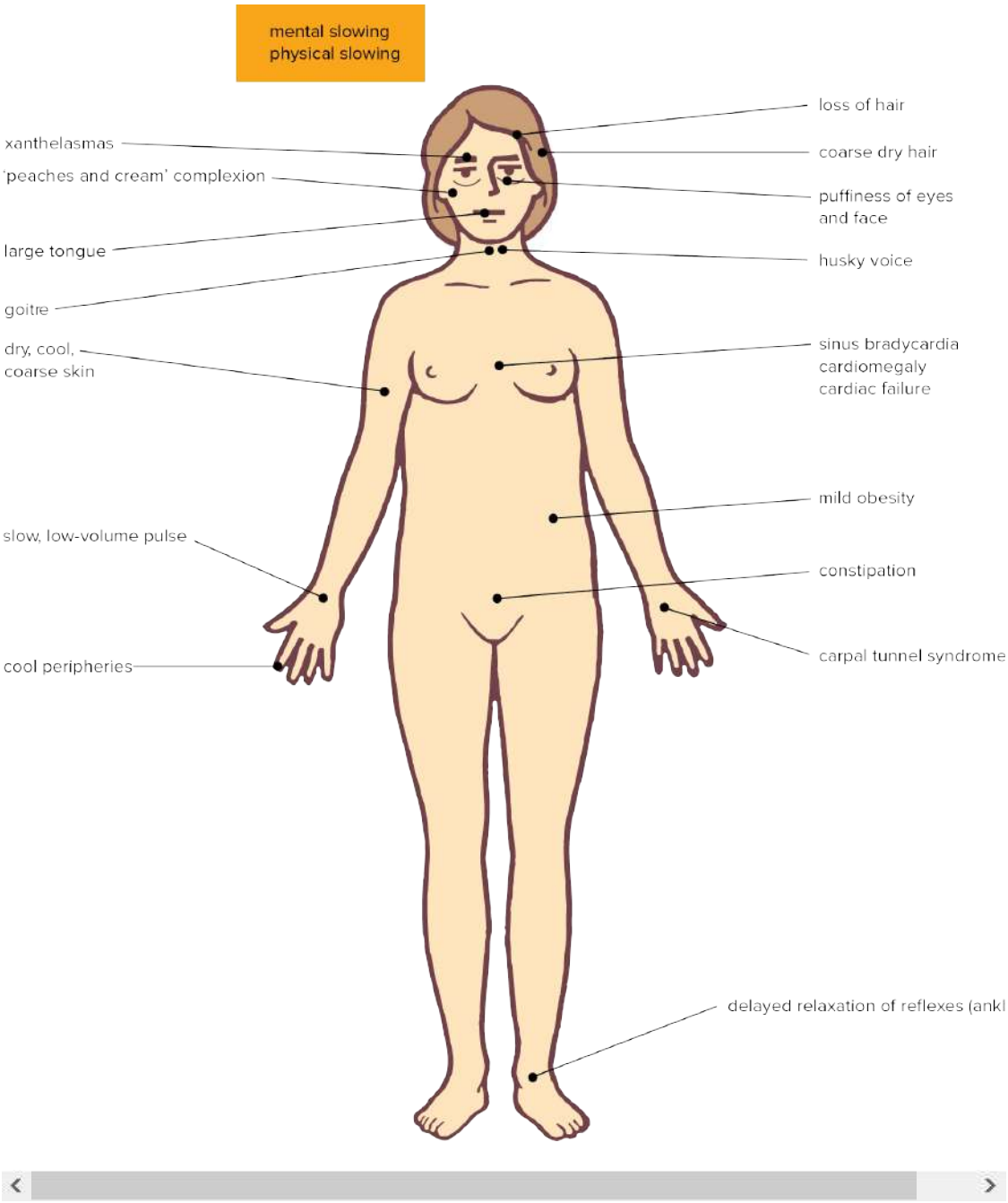

FIGURE 14.2 Clinical features of hypothyroidism

Other diverse presentations of thyroid disorders are given in TABLE 14.2 .

Table 14.2 Various diverse presentations of thyroid disorders[3,5]

	Hypothyroidism	Hyperthyroidism

General	Lethargy, tiredness Dry skin Husky voice	Weakness Sweaty skin, especially hands
Psychiatric	Depression Dementia Psychosis (myxoedema madness)	Anxiety/irritability Hyperkinesis Psychosis
Musculoskeletal	Myofibrositis Myalgia Joint effusions	Muscle weakness Proximal myopathy
Skin	Dry, cool skin Vitiligo	Warm, thin, soft, moist skin Vitiligo Pretibial myxoedema
Cardiovascular	Ischaemia Cardiomegaly Pericardial effusion Bradycardia Hyperlipidaemia	Tachycardia Atrial fibrillation Heart failure/breathlessness Systolic hypertension
Endocrine	Galactorrhoea Goitre Infertility	Goitre Gynaecomastia
Gynaecological	Menstrual irregularity Menorrhagia (mainly) Oligomenorrhoea	Other menstrual disturbances Oligomenorrhoea
Neurological	Neuropathy Nerve entrapment (e.g. carpal tunnel) Ataxia	Periodic paralysis Tremor
Haematological	Anaemia	–
Emergency	Myxoedema coma Postanaesthetic hypoventilation	Thyroid crisis
Other	Reduced libido Weight gain	Reduced libido Eye signs

Cold intolerance	Fever (uncommon)
Constipation	Onycholysis
	Premature grey hair
	Weight loss

Hashimoto thyroiditis (autoimmune thyroiditis)

Hashimoto thyroiditis, or lymphocytic thyroiditis, which is an autoimmune thyroiditis, is the commonest cause of bilateral non-thyrotoxic goitre in Australia. Features are:

- bilateral goitre
- classically described as firm and rubbery
- patients may be hypothyroid or euthyroid with a possible early period of thyrotoxicosis

Diagnosis is confirmed by a strongly positive antithyroid microsomal antibody (TPO Ab) titre and/or fine-needle aspiration cytology.[4]

Hashimoto thyroiditis may present as postpartum hypothyroidism. The hypothyroidism may resolve in 6–12 months or may be permanent.[4]

Laboratory diagnosis of hypothyroidism

Thyroid function tests (see TABLE 14.1):

- T_4—subnormal
- TSH—elevated (>10 is clear gland failure)

If T_4 is low and TSH is low or normal, consider pituitary dysfunction (secondary hypothyroidism) or sick euthyroid syndrome. A raised TSH and T_4 in normal range denotes ‘subclinical’ hypothyroidism and treatment is appropriate albeit controversial.[2,3]

Interpretation of TFTs can be difficult but requires matching to the clinical ‘picture’ and consultant advice.

Other tests

- Serum cholesterol level elevated
- Anaemia: usually normocytic; may be macrocytic
- ECG: sinus bradycardia, low voltage, flat T waves

Management[6,7,8]

Confirm the diagnosis, provide appropriate patient education and refer the patient where appropriate.

Exclude coexisting hypoadrenalism and ischaemic heart disease before T_4 replacement.

Note: Treatment as primary hypothyroidism when hypopituitarism is the cause may precipitate adrenal crisis.

Thyroid medication

- Levothyroxine (thyroxine) 50–100 mcg daily, increasing by 25 mcg up to 100–200 mcg if required

Note: Start with low doses (25–50 mcg daily) in >60 years and those with ischaemic heart disease and 50–100 mcg in others. Avoid overdosage.

- Aim to achieve TSH levels of 0.5–2 mU/L.
- Monitor TSH levels 6–8 weeks at first. As euthyroidism is achieved, monitoring may be less frequent (e.g. 2–3 months). When stable on optimum dose of T_4, monitor every 2–3 years. Treatment is usually lifelong.

Special treatment considerations

- *Ischaemic heart disease.* Rapid thyroxine replacement can precipitate myocardial infarction, especially in the elderly.
- *Pregnancy and postpartum.* Continue thyroxine during pregnancy; watch for hypothyroidism (an increased dose of T_4 is often required).
- *Elective surgery.* If euthyroid, can stop thyroxine for one week. If subthyroid, defer surgery until euthyroid.
- *Myxoedema coma.* Urgent hospitalisation under specialist care is required. Intensive treatment is required, which may involve parenteral T_4 or T_3 as liothyronine or thyroxine by slow IV injection.

Myxoedema coma

This is a life-threatening emergency with coma, extreme hyperthermia, areflexia and respiratory depression. Precipitating factors include illness, infection, trauma and cold. Treatment is supportive care, IV thyroxine or liothyronine and corticosteroids. Convert to oral T_4 when stable.

Neonatal hypothyroidism

Misdiagnosing this serious condition leads to failure to thrive, retarded growth and poor school performance. If untreated it leads to permanent intellectual damage (cretinism). The clinical features of the newborn include coarse features, dry skin, supra-orbital oedema, jaundice, harsh cry, slow feeding and umbilical hernia. It is detected by routine neonatal heel-prick blood testing. Thyroxine replacement should be started as soon as possible, at least before 2 weeks of age, to avert intellectual retardation.

When to refer—hypothyroidism[5,7]

- Doubt about diagnosis, diagnostic tests or optimum replacement dosage
- Apparent secondary hypothyroidism, severe illness and associated ischaemic heart disease
- Concurrent autoimmune disease
- Hypothyroidism with goitre, postpartum thyroid dysfunction and in the neonate
- Myxoedema coma

Hyperthyroidism (thyrotoxicosis)

Hyperthyroidism is also relatively common and may affect up to 2% of women, who are affected four to five times more often than men (see FIG. 14.3). Graves disease is the most common cause, followed closely by nodular thyroid disease.

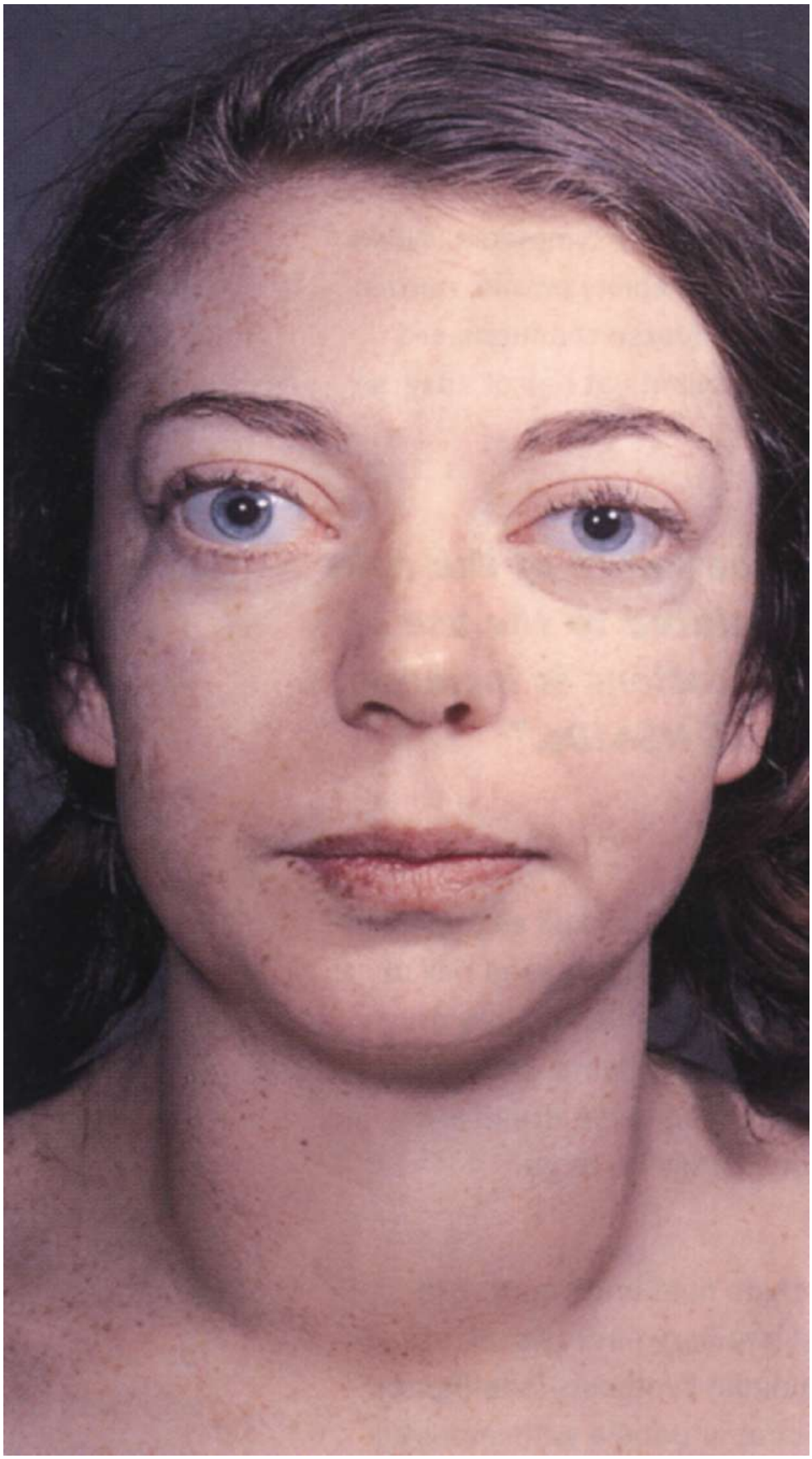

FIGURE 14.3 Thyrotoxicosis patient with exophthalmos and goitre

Photo courtesy Duncan Topliss

Causes[4,9]

- Graves disease (typical symptoms with a diffuse goitre and eye signs)
- Autonomous functioning nodules/toxic adenoma
- Subacute thyroiditis (de Quervain thyroiditis)—viral origin (suspect if painful thyroid and malaise)
- Excessive intake of thyroid hormones—thyrotoxicosis factitia
- Exogenous iodine excess, e.g. food contamination
- Amiodarone (beware of this drug)

Key facts and checkpoints

- The classic symptoms may be lacking in elderly patients who may have only cardiovascular manifestations (e.g. unexplained heart failure or cardiac arrhythmias).
- Care has to be taken not to dismiss hyperthyroidism as severe anxiety.

Clinical features

- Heat intolerance
- Sweating of hands
- Muscle weakness
- Weight loss despite normal or increased appetite
- Emotional lability, especially anxiety, irritability
- Palpitations
- Frequent loose bowel motions

DxT anxiety + weight loss + weakness → thyrotoxicosis

Physical examination

See FIGURE 14.4 . Signs are (usually):

- agitated, restless patient
- warm and sweaty hands
- fine tremor (place paper on hands)
- goitre
- proximal myopathy
- hyperactive reflexes
- bounding peripheral pulse
- ± atrial fibrillation

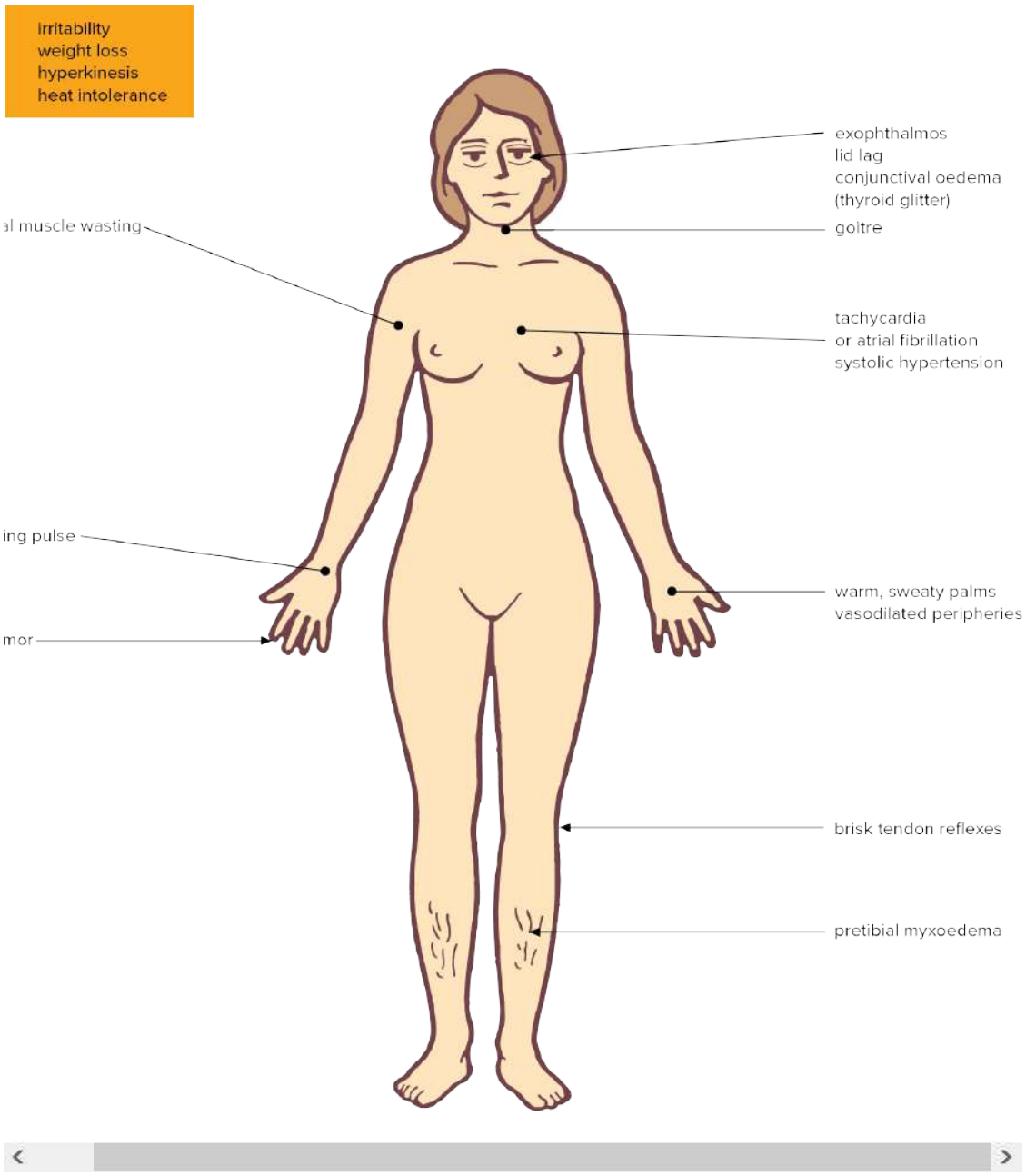

FIGURE 14.4 Clinical features of hyperthyroidism

Eye signs

- Lid retraction (small area of sclera seen above iris)
- Lid lag
- Exophthalmos
- Ophthalmoplegia in severe cases

Investigations

- T_4 (and T_3) elevated
- TSH level suppressed
- Radioisotope scan
- Antithyroid peroxidase (TPO Ab)—often positive

The isotope scan enables a diagnosis of Graves disease to be made when the scan shows uniform increased uptake. Increased irregular uptake would suggest a toxic multinodular goitre, while there is poor or no uptake with de Quervain thyroiditis and thyrotoxicosis factitia.

Management

- Establish the precise cause before initiating treatment.
- Refer to an endocrinologist to guide treatment.
- Educate patients and emphasise the possibility of development of recurrent hyperthyroidism or hypothyroidism and the need for lifelong monitoring.
- Monitor for cardiovascular complications, osteoporosis and eye problems.

Treatment[10,7,8]

- Radioactive iodine therapy (^{131}I)
- Thionamide antithyroid drugs (initial doses)

  carbimazole 10–45 mg (o) daily starting with 10–20 mg in divided doses depending on disease activity

  or

  propylthiouracil 200–600 mg (o) daily in divided doses or methimazole

- Adjunctive drugs

  beta blockers (for symptoms in acute florid phase, e.g. propranolol 10–40 mg, 6 to 8 hourly); diltiazem or atenolol are alternatives

  lithium carbonate (rarely used when there is intolerance to thionamides)

  Lugol's iodine: mainly used prior to surgery

- Surgery

subtotal thyroidectomy

or

total thyroidectomy

Treatment (Graves disease)

There is no ideal treatment and selection of antithyroid drugs, radioiodine or surgery depends on many factors, including age, size of goitre, social and economic factors and complications of treatment. Encourage cessation of smoking.

Guidelines[10,8]

- Younger patients with small goitres and mild case—18-month course antithyroid drugs
- Older patients with small goitres—as above or radioiodine (preferably when euthyroid)
- Large goitres or moderate-to-severe cases—antithyroid drugs until euthyroid, then surgery or ^{131}I
- In Australia (as in the US) ^{131}I is being increasingly used

Treatment (autonomous functioning nodules and toxic adenoma)

Control hyperthyroidism with antithyroid drugs, then surgery or ^{131}I. Long-term remissions on antithyroid drugs in a toxic nodular goitre are rare.

Subacute thyroiditis (de Quervain thyroiditis)[8]

Hyperthyroidism is usually transient for 1–2 months, and follows a surge of thyroxine after a viral-type illness, then followed by hypothyroidism for 4–6 months. Symptoms include pain and/or tenderness over the goitre (especially on swallowing), fever, ESR elevated, TPO Ab low or absent and radionuclide scan near absent uptake. In the acute phase treatment is based on rest, analgesics (aspirin 600 mg (o) 4–6 hourly) or ibuprofen 200–400 mg (o) and soft foods. Rarely, when pain is severe, corticosteroids (e.g. prednisolone) may be used. Antithyroid drugs are not indicated but beta blockers can be used to control symptoms.

Painless postpartum thyroiditis

Release of thyroid hormone from autoimmune destruction of thyroid. Typically 1–6 months post delivery. Hyperthyroidism initially, followed by hypothyroidism. Diffuse small goitre, poor radionuclide uptake, high TPO Ab. Treat with beta blockers for symptoms and thyroxine for hypothyroid phase.

Note: Autoimmune destruction of the thyroid with thyroiditis—painless or painful—can lead to

agranulocytosis, so monitor for signs of fever or mouth ulcers.

Thyroid crisis (thyroid storm)[8]

Clinical features are marked anxiety, weight loss, weakness, proximal muscle weakness, hyperpyrexia, tachycardia (>150 per minute), heart failure and arrhythmias. It is usually precipitated by surgery or an infection in an undiagnosed patient.

It requires urgent intensive hospital management with antithyroid drugs; IV saline infusion, IV corticosteroids, anti-heart failure and antiarrhythmia therapy, especially beta blockers.

When to refer—hyperthyroidism[9]

- Doubt about the diagnosis
- Severe hyperthyroidism, especially if there is coexisting thyrocardiac disease
- Pregnant patients with hyperthyroidism
- Progression of exophthalmos; eye disease
- Ideally all cases

Goitre

Thyroid enlargement may be diffuse or multinodular. Diffuse causes include physiological, Graves disease, thyroiditis (Hashimoto or de Quervain), iodine deficiency or it can be hereditary.

Investigations include TFTs, needle biopsy, ultrasound and CXR. Management is supportive; thyroxine if TSH elevated (may lead to marked regression) and subtotal or total thyroidectomy.

Thyroid nodules

A thyroid nodule is defined as a discrete lesion on palpation and/or ultrasonography that is distinct from the rest of the thyroid gland.

Causes

- Dominant nodule in a multinodular goitre (most likely)
- Colloid cyst
- True solitary nodule: adenoma, carcinoma (papillary or follicular)

Investigations

- Ultrasound imaging
- Fine-needle aspiration cytology
- Thyroid function tests

Thyroid carcinoma[8]

The main presentations are a painless nodule, a hard nodule in an enlarged gland or lymphadenopathy. Papillary carcinoma is the most common malignancy. Although rare compared with non-malignant lesions (such as colloid nodules, cysts, haemorrhage and benign adenomas), it is important not to miss carcinoma because of the very high cure rate with expert-directed treatment. This often involves total thyroidectomy, ablative ^{131}I treatment, thyroxine replacement and follow-up with serum thyroglobulin measurements, ^{131}I/thallium scanning and neck ultrasound. Fine-needle aspiration is the investigation of choice.

Pituitary disorders

Pituitary tumours[9]

These account for 10% of intracranial tumours and are invariably benign adenomas. They can present with hormone deficiencies, features of hypersecretory syndromes (e.g. prolactin, GH, ACTH) or by local tumour mass symptoms (e.g. headache, visual field loss, seizures, cranial nerve 3, 4, 6 palsy).

Hyperprolactinaemia[11]

The main causes (of many) are a pituitary adenoma (prolactinoma; micro- or macro), pituitary stalk damage, drugs—such as antipsychotics, various antidepressants, metoclopramide, cimetidine, oestrogens, opiates, marijuana—and physiological causes such as pregnancy and breastfeeding.

Clinical features

- Symptoms common to males and females: reduced libido, subfertility, galactorrhoea (mainly females)
- Females: amenorrhoea/oligomenorrhoea
- Males: erectile dysfunction, reduced facial hair

Diagnosis

- Serum prolactin and macroprolactin assays

- MRI: consider if headache, etc

Refer for management, which may include a dopamine agonist such as cabergoline or bromocriptine, surgical resection (rarely necessary) or radiotherapy.

Acromegaly

Symptoms suggestive of acromegaly include:

- excessive growth of hands (increased glove size)
- excessive growth of tissues (e.g. nose, lips, face)
- excessive growth of feet (increased shoe size)
- increased size of jaw and tongue; kyphosis
- general: weakness, sweating, headaches
- sexual changes, including amenorrhoea and loss of libido
- disruptive snoring (sleep apnoea)
- deepening voice

> **DxT** nasal problems + fitting problems (e.g. rings, shoes) + sweating → acromegaly

Diagnosis[9,12]

- Plasma growth hormone excess
- Elevated insulin-like growth factor 1 (IGF-1) (somatomedin)—the key test
- X-ray skull and hands
- MRI scanning pituitary
- Consider associated impaired glucose tolerance/diabetes

Obtain old photographs (if possible).

Treatment options: transsphenoidal pituitary microsurgery, drugs and radiotherapy.

Diabetes insipidus and SIADH

Impaired secretion of vasopressin (antidiuretic hormone) from the posterior pituitary leads to

polyuria, nocturia and compensatory polydipsia, resulting in the passage of 3–20 L of dilute urine per day. There are several causes of diabetes insipidus (DI), the commonest being postoperative (hypothalamic-pituitary), which is usually transient only. Other causes of cranial DI include tumours, infections and infiltrations. In nephrogenic DI the kidney tubules are insensitive to vasopressin. Differential diagnosis includes compulsive (psychogenic) water drinking. The syndrome of secretion of inappropriate antidiuretic hormone (SIADH) is caused by cancer (e.g. lung, lymphomas, kidney, pancreas), pulmonary disorders, various intracranial lesions and drugs such as carbamazepine and many antipsychotic agents. Management of SIADH is essentially fluid restriction.

The treatment of DI is desmopressin, usually given twice daily intranasally.

DxT weakness + polyuria + polydipsia → diabetes insipidus

Hypopituitarism[8]

This rare disorder (acute or chronic) should be considered with:

- a history of postpartum haemorrhage or head injury
- symptoms of hypothyroidism
- symptoms of adrenal insufficiency
- symptoms suggestive of a pituitary tumour
- thin, wrinkled skin: ‘monkey face’
- pale ‘alabaster’ skin/hairlessness

Causes: pituitary adenoma, other parasellar tumours and inflammatory/infiltrative lesions.

DxT (female): amenorrhoea + loss of axillary and pubic hair + breast atrophy → hypopituitarism

DxT (male): ↓ libido + impotence + loss of body hair → hypopituitarism

Investigate with serum pituitary hormones, imaging (MRI) and triple stimulation test.

Treatment includes HRT, surgery or radiotherapy.

Adrenal disorders

The primary zones of the adrenal gland and their secretions

Cortex

- Zona glomerulosa—mineral corticoids, especially aldosterone
- Zona fasciculata—glucocorticoids
- Zona reticularis—androgens, especially DHEA

Medulla

- Catecholamines—epinepherine, norepinephrine

It is worth keeping in mind these uncommon disorders of the adrenal gland which can be difficult to diagnose in the early stages, namely:

- chronic adrenal insufficiency (Addison disease)—deficiency of cortisol and aldosterone
- Cushing syndrome—cortisol excess
- primary hyperaldosteronism (refer to CHAPTER 77)

Addison disease[8,13]

Autoimmune destruction of the adrenals is the most common cause; others are infection, e.g. TB or fungal.

Clinical features

- Lethargy/excessive fatigue/weakness
- Anorexia and nausea
- Diarrhoea/abdominal pain
- Weight loss
- Dizziness/funny turns, syncope: hypoglycaemia (rare); postural hypotension (common)
- Hyperpigmentation, especially mucous membranes of mouth and hard palate, skin creases of hands

If Addison disease remains undiagnosed, wasting leading to death may occur. Severe dehydration can be a feature. Delayed diagnosis is a huge problem. Hypertension and heart failure requires careful monitoring.

DxT fatigue + a/n/v + abdominal pain (± skin discolouration) → Addison disease

Diagnosis

- Elevated serum potassium, low serum sodium
- Low plasma cortisol level (fails to respond to synthetic adrenocorticotropic hormone [ACTH])
- The short synacthen stimulation test is the definitive test
- Consider adrenal autoantibodies and imaging? calcification of adrenals

Treatment: corticosteroid replacement—hydrocortisone/fludrocortisone acetate, other options.

Addisonian crisis[8,13]

An Addisonian crisis develops because of an inability to increase cortisol in response to stress, which may include intercurrent infection, surgery or trauma.

Clinical features

- Nausea and vomiting
- Acute abdominal pain
- Severe hypotension progressing to shock
- Weakness, drowsiness progressing to coma

Urgent management[13]

- Establish IV line with IV fluids
- Hydrocortisone sodium succinate 100 mg IV initially and 50–100 mg 4–6 hourly until stable
- Arrange urgent hospital admission

Cushing syndrome[8]

The five main causes are:

- iatrogenic—chronic corticosteroid administration
- pituitary ACTH excess (Cushing disease)
- bilateral adrenal hyperplasia
- adrenal tumour (adenoma, adenocarcinoma)
- ectopic ACTH or (rarely) corticotrophin-releasing hormone (CRH) from non-endocrine tumours (e.g. oat cell carcinoma of lung)

The clinical features are caused by the effects of excess cortisol and/or adrenal androgens.

Clinical features

- Proximal muscle wasting and weakness
- Central obesity, buffalo hump on neck
- Cushing facies: plethora, moon face, acne
- Weakness
- Hirsutism
- Abdominal striae
- Thin skin, easy bruising
- Hypertension
- Hyperglycaemia (30%)
- Menstrual changes (e.g. amenorrhoea)
- Osteoporosis
- Psychiatric changes, especially depression
- Backache

DxT plethoric moon face + thin extremities + muscle weakness → Cushing syndrome

Diagnosis (apart from iatrogenic cause)

- Cortisol excess (plasma or 24-hour urinary cortisol)

- Dexamethasone suppression test
- Late night salivary cortisol (2 measurements)
- Inferior petrosal sinus sampling
- Serum ACTH
- Radiological localisation: MRI for ACTH-producing pituitary tumours; CT scanning for adrenal tumours

Management

Ideally transsphenoidal excision of pituitary tumour. Pharmacological blockade of corticosteroid production may be necessary, ketoconazole (o) is first line.

Primary hyperaldosteronism[8]

Most commonly due to an adrenal adenoma.

Conn syndrome

Usually asymptomatic and hypertensive but any symptoms are features of hypokalaemia:

- weakness, headaches
- palpitations
- cramps
- paraesthesia
- polyuria and polydipsia

Investigations

- Aldosterone (serum and urine) ↑
- Plasma renin ↓
- Plasma aldosterone to renin activity ratio
- Na ↑, K ↓, alkalosis
- Imaging (MRI or CT scan) of adrenals

Refer for treatment including possible surgery to excise adenoma. Spironolactone to prepare for surgery.

Phaeochromocytoma[8,12]

A dangerous tumour of the adrenal medulla. Clinical features are paroxysms or spells of:

- anxiety
- hypertension
- headache (throbbing); tremor
- sweating
- palpitations
- pallor/skin blanching
- rising sensation of tightness in upper chest and throat (angina can occur)

DxT episodic headache + sweating + tachycardia → phaeochromocytoma

Investigations

- Series of three 24-hour free catecholamines ↑ VMA
- Abdominal CT or MRI scan (both highly sensitive)

Treatment

- Excise tumour, cover with alpha and beta blockers

Congenital adrenal hyperplasia (adrenogenital syndrome)[6,8]

An AR condition with 21-hydroxylase deficiency being the most common of several forms. There is inadequate synthesis of cortisol and aldosterone with increased androgenisation. Major problem is adrenal failure ± salt-losing state (SLS). In females, ambiguity of external genitalia and hirsutism before puberty usually occurs. Males may have normal urogenital development but SLS is a concern. Infants of either sex may present with failure to thrive or vomiting and dehydration (SLS). Lifelong glucocorticoid treatment (e.g. prednisolone) is required. Wearing an alert bracelet or necklace is strongly recommended for these patients (www.medicalert.org.au).[6]

Adrenal tumours[9]

Most of those detected by abdominal imaging are benign and termed ‘incidentalomas’ but

serious tumours include adrenal carcinoma, phaeochromocytoma, neuroblastoma, glucocorticoid or a mineralocorticoid secreting tumour.

Rule: tumours >4 cm require thorough assessment as malignant tumours are large. Excision is usually advisable.

Incidentalomas

These are adrenal tumours ≥1 cm. Most are benign and non-functioning. An important issue is malignancy, and if this is the case, whether it is primary, secondary or functional (hormone secreting).

Investigations to consider include electrolytes, aldosterone/renin ratio, catecholamines, testosterone, DHEAs, dexamethasone suppression test, CT scan. Surgical excision should be considered under specialist guidance.

Calcium disorders

Hypercalcaemia[12,14]

Suspect hypercalcaemia if there is weakness, tiredness, malaise, anorexia, nausea or vomiting, abdominal pain, loin pain, constipation, thirst, fever, polyuria, drowsiness, dizziness, personality changes, muscle aches and pains, visual disturbances. Measure urea and electrolytes (especially calcium), creatinine, albumin.

Primary hyperparathyroidism, familial hypercalciuric hypercalcaemia and neoplasia, especially carcinoma of lung and breast (with metastases to bone), account for over 90% of cases. Other causes include Paget disease, Williams syndrome, prolonged immobilisation, dehydration, sarcoidosis and milk-alkali syndrome. Investigations include ESR, serum parathyroid hormone (N: 1.0–7 pmol/L), serum ACE levels, serum alkaline phosphatase, chest X-ray, Sestamibi scan and bone scan. Requires specialist referral.

DxT weakness + constipation + polyuria → hypercalcaemia

DxT cramps + confusion + tetany → hypocalcaemia

Primary hyperparathyroidism[12]

Hyperparathyroidism is caused by an excessive secretion of parathyroid hormone and is usually due to a parathyroid adenoma. The classic clinical features of hyperparathyroidism are due to the

effects of hypercalcaemia. Rarely, a parathyroid crisis in a misdiagnosed patient may result in death from severe hypercalcaemia.

> Classic mnemonic: bones, moans, stones, abdominal groans

Diagnosis

- Exclusion of other causes of hypercalcaemia
- Serum parathyroid hormone (elevated)
- TC-99m Sestamibi scan to detect tumour

Treatment

Refer for possible surgical management.

Hypocalcaemia[8,14]

Causes include parathyroid injury, autoimmune hyperparathyroidism, severe vitamin D deficiency and neonates of mothers with hypercalcaemia. This usually presents with tetany or more generalised neuromuscular hyperexcitability and neuropsychiatric manifestations. The sensory equivalents are paraesthesia in the hands, feet and around the mouth (distinguish from tetany seen in the respiratory alkalosis of hyperventilation). There may be seizures and cramps. The diagnosis is by measurement of serum total calcium concentration in relation to serum albumin (s. calcium <2.10 mmol/L).

Two important signs are:

- Trousseau sign: occlusion of the brachial artery with BP cuff precipitates carpopedal spasm (wrist flexion and fingers drawn together)
- Chvostek sign: tapping over parotid (facial nerve) causes twitching in facial muscles

Treatment involves careful adjustments in dosage of calcitriol and calcium to correct hypocalcaemia and avoid hypercalcaemia and hypercalciuria (the latter may lead to kidney impairment).

Hypoparathyroidism

Hypoparathyroidism is the most common cause of hypocalcaemia. Causes include postoperative thyroidectomy and parathyroidectomy, congenital deficiency (DiGeorge syndrome) and idiopathic (autoimmune) hypoparathyroidism. The main features are neuromuscular hyperexcitability, tetany and neuropsychiatric manifestations.

Other electrolyte disturbances

Hypernatraemia Na^+ >145 mmol/L

Causes

- Water depletion (e.g. diabetes insipidus)
- Water and sodium depletion (e.g. diarrhoea)
- Corticosteroid excess (e.g. Cushing syndrome, Conn syndrome)
- Iatrogenic: excess IV hypertonic Na solutions

Clinical features

- Thirst, confusion, lethargy, weakness, irritability, oliguria
- Orthostatic hypotension
- Muscle twitching or cramps
- Signs of dehydration
- Severe: seizures, delirium, hyperthermia, coma

Hyponatraemia Na^+ <135 mmol/L

Causes

- Water retention (e.g. CCF, hypoalbuminaemia)
- Kidney failure to conserve salt (e.g. nephritis, diabetes mellitus, Addison disease)
- Gastrointestinal loss of Na^+ (e.g. vomiting, diarrhoea)
- Drugs (e.g. diuretic excess, ACE inhibitors)

Clinical features

- Asymptomatic when mild
- Anorexia, nausea, lethargy, confusion, headache, ataxia, mental changes (e.g. in personality)
- Severe: convulsions, coma, death

Hyperkalaemia K^+ >5.5 mmol/L

The first sign of hyperkalaemia (e.g. >6) may be a cardiac arrest. A medical emergency if >6.5.

Causes

- Oliguria, kidney failure
- Acidosis (especially metabolic)
- Mineralocorticoid deficiency: Addison disease, aldosterone antagonists
- Excessive intake of K^+ (e.g. IV fluids with K)
- Drugs (e.g. spironolactone, ACE inhibitors, NSAIDs, suxamethonium)
- Consider artefact, e.g. haemolysed sample

Clinical features

- Malaise, muscle weakness, flaccid paralysis (rare)
- May be asymptomatic until cardiac toxicity
- May cause cardiac arrest—asystole or fibrillation
- ECG: peaked T waves, ↓ QT, ↑ PR interval → arrhythmias

Hypokalaemia K^+ <3.5 mmol/L

If <2.5 severe symptoms, seek urgent attention.

Causes

- Kidney disease
- Gastrointestinal loss: vomiting, diarrhoea
- Alkalosis
- Mineralocorticoid excess
- Loss of extracellular fluid to intracellular (e.g. burns, other trauma, pyloric stenosis)
- Drugs (e.g. diuretics: frusemide, thiazides), purgatives, liquorice abuse
- Reduced intake of K^+

Clinical features

- Lethargy, muscle weakness and cramps, mental lethargy and confusion
- Severe flaccid paralysis, tetany, coma
- ECG: prominent U waves, depressed ST segment, T waves, arrhythmias

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Hyperthyroidism
- Hypothyroidism
- Goitre (thyroid swelling)

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15 Spinal dysfunction

The spine is an ordered series of bones running down your back. You sit on one end of it, sometimes too hard with ill effect, and your head sits on the other. Poor spine—what a load.

ANON, 19TH CENTURY

Spinal or vertebral dysfunction can be regarded as a masquerade mainly because the importance of the spine as a source of various pain syndromes has not been emphasised in medical training. Practitioners whose training and treatment are focused almost totally on the spine may swing to the other extreme and some may attribute almost every clinical syndrome to dysfunction of spinal segments. The true picture lies somewhere in between.

The diagnosis is straightforward when the patient is able to give a history of a precipitating event such as lifting, twisting the neck or having a motor vehicle accident, and can then localise the pain to the midline of the neck or back. The diagnostic problem arises when the pain is located distally to its source, whether it is radicular (due to pressure on a nerve root) or referred pain. The problem applies particularly to pain in anterior structures of the body.

If a patient has pain anywhere, it is possible that it could be spondylogenic and practitioners should always keep this in mind.

The various syndromes caused by spinal dysfunction will be presented in more detail under neck pain, thoracic back pain and lumbar back pain.

Cervical spinal dysfunction[1]

The cervical spine is the origin of many confusing clinical problems and syndromes.

Clinical problems of cervical spinal origin

Pain originating from disorders of the cervical spine is usually, although not always, experienced in the neck. The patient may experience headache or pain around the ear, face, arm, shoulder, upper anterior or posterior chest.[2]

Possible symptoms:

- neck pain
- neck stiffness
- headache
- ‘migraine’-like headache
- facial pain
- arm pain (referred or radicular)
- myelopathy (sensory and motor changes in arms and legs)
- ipsilateral sensory changes of scalp
- ear pain (peri-auricular)
- scapular pain
- anterior chest pain
- torticollis
- dizziness/vertigo
- visual dysfunction

FIGURE 15.1 indicates typical directions of referred pain from the cervical spine. Pain in the arm (brachialgia) is common and tends to cover the shoulder and upper arm as indicated.

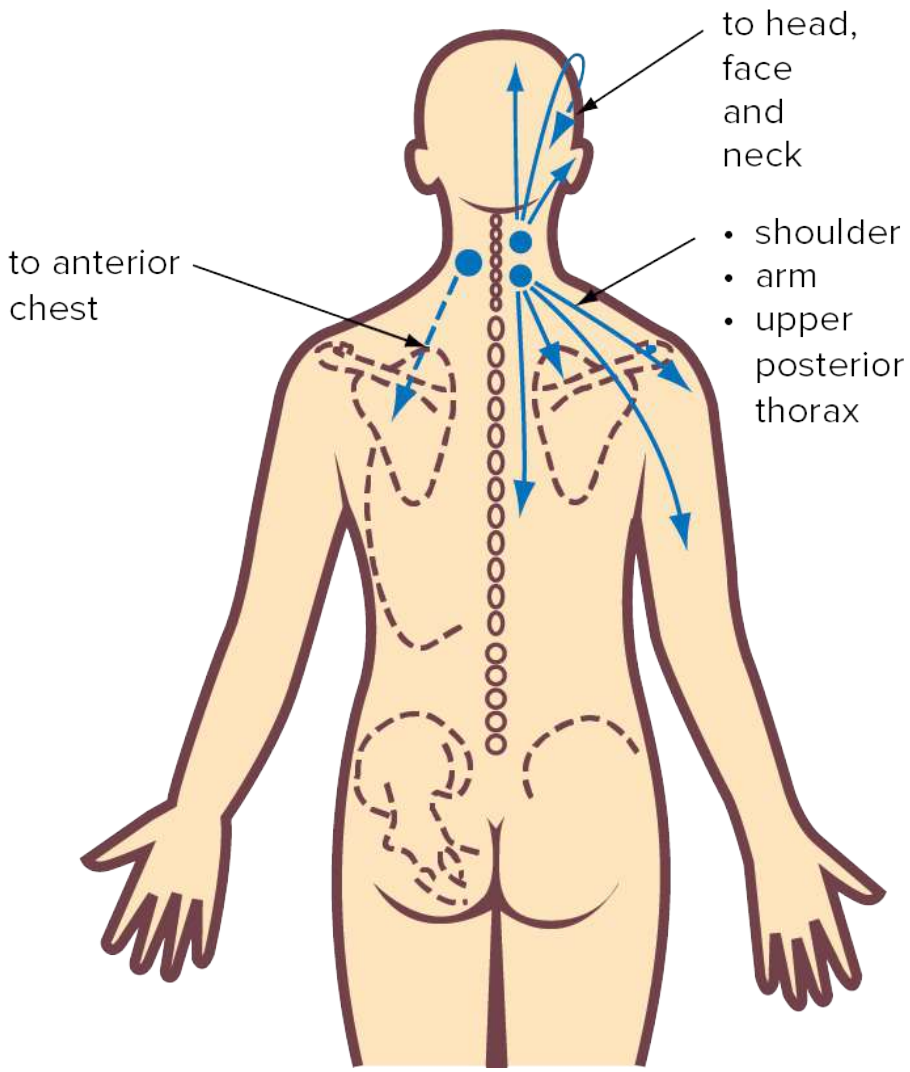


FIGURE 15.1 Possible directions of referred pain from the cervical spine

If the cervical spine is overlooked as a source of pain (such as in the head, shoulder, arm, upper chest—anterior and posterior—and around the ear or face) the cause of the symptoms will remain masked and mismanagement will follow.

Dysfunction of the cervical spine can cause many unusual symptoms such as headache and vertigo, a fact that is often not recognised. Despite teaching to the contrary from some, the cervical spine is a common cause of headache, especially dysfunction of the facet joints at the C1–2 and C2–3 levels. The afferent pathways from these levels share a common pathway in the brain stem as the trigeminal nerve, hence the tendency for pain to be referred to the head and the face (see CHAPTER 41).

Manipulation of the cervical spine can be a dramatically effective technique, but it should be used with care and never used in the presence of organic disease and vertebrobasilar insufficiency. It should, therefore, be given only by skilled therapists. Two groups at special risk

from quadriplegia are those with rheumatoid arthritis of the neck and Down syndrome, because of the instability of the odontoid process.

However, good results can be achieved by gentler techniques, such as mobilisation and muscle energy therapy (refer to CHAPTER 51).

Thoracic spinal dysfunction

The most common and difficult masquerades related to spinal dysfunction occur with disorders of the thoracic spine (and also the low cervical spine), which can cause vague aches and pains in the chest, including the anterior chest. This applies particularly to unilateral pain.

Pain in the thoracic spine with referral to various parts of the chest wall and upper abdomen is common in all ages and can closely mimic the symptoms of visceral disease, such as angina pectoris and biliary colic (see TABLE 15.1). If a non-cardiac cause of chest pain is excluded, then the possibility of referral from the thoracic spine should be considered in the differential diagnosis.[3] People of all ages can experience thoracic problems and it is surprisingly common in young people, including children.

Table 15.1 Conditions mimicked by thoracic spinal dysfunction (usually unilateral pain)

Cardiovascular
Acute coronary syndromes
Angina
Pericarditis
Dissecting aneurysm
Chest/respiratory
Pleurisy
Pneumothorax
Carcinoma lung, esp. mesothelioma
Pulmonary infarction
Tuberculosis
Fractured rib, esp. cough fracture
Renal
Renal colic
Urinary infection/pyelonephritis
Gastrointestinal
Biliary colic
Appendicitis

Diverticulitis
Others
Herpes zoster
Epidemic pleurodynia (Bornholm disease)
Precordial catch (stitch in side)
Costochondritis
Hernia (symptomatic)
Muscular tears

Pain of thoracic spinal origin may be referred anywhere to the chest wall, but the commonest sites are the scapular region, the paravertebral region 2–5 cm from midline and, anteriorly, over the costochondral region (see FIG. 15.2).

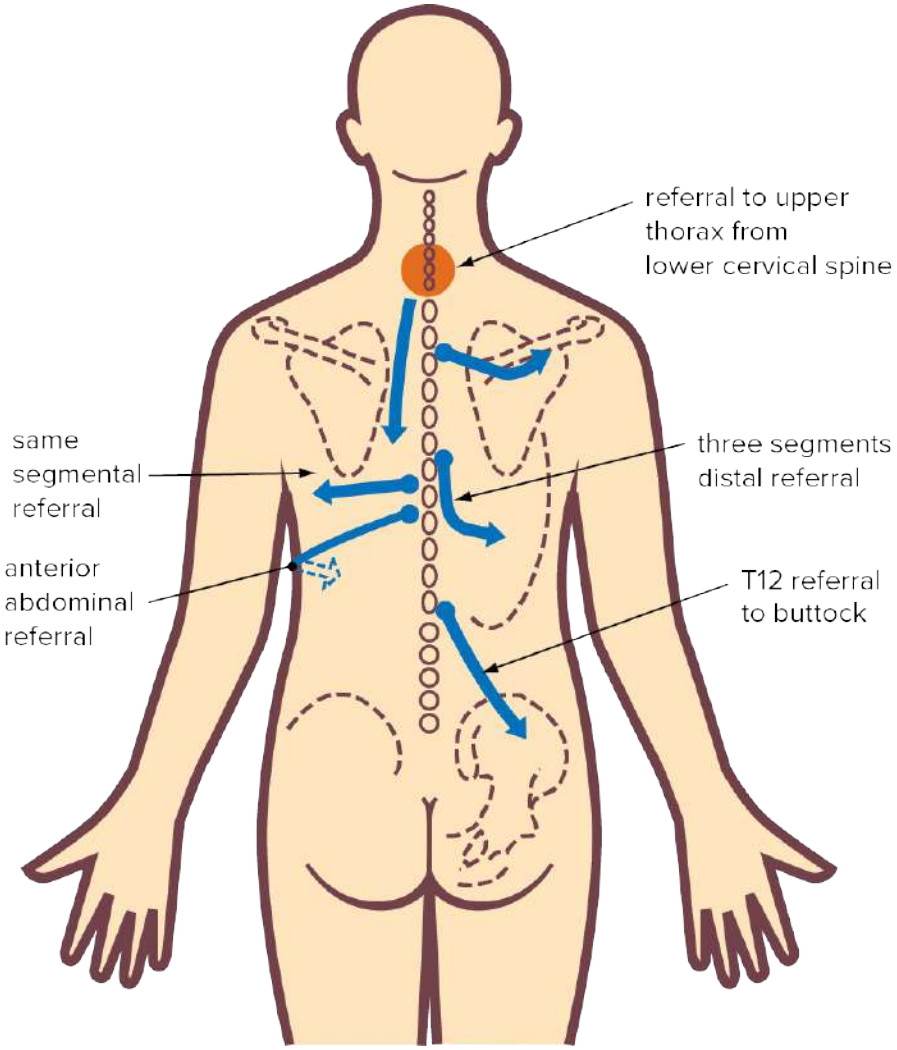


FIGURE 15.2 Examples of referral patterns for the thoracic spine

Thoracic pain of lower cervical origin[4]

The clinical association between injury to the lower cervical region and upper thoracic pain is well known, especially with ‘whiplash’ injuries. It should be noted that the C4 dermatome is in close proximity to the T2 dermatome.

The T2 dermatome appears to represent the cutaneous areas of the lower cervical segments, as the posterior primary rami of C5, C6, C7, C8 and T1 innervate musculature and have no significant cutaneous innervation.

The pain from the lower cervical spine can also refer pain to the anterior chest, and mimic coronary ischaemic pain. The associated autonomic nervous system disturbance can cause considerable confusion in making the diagnosis.

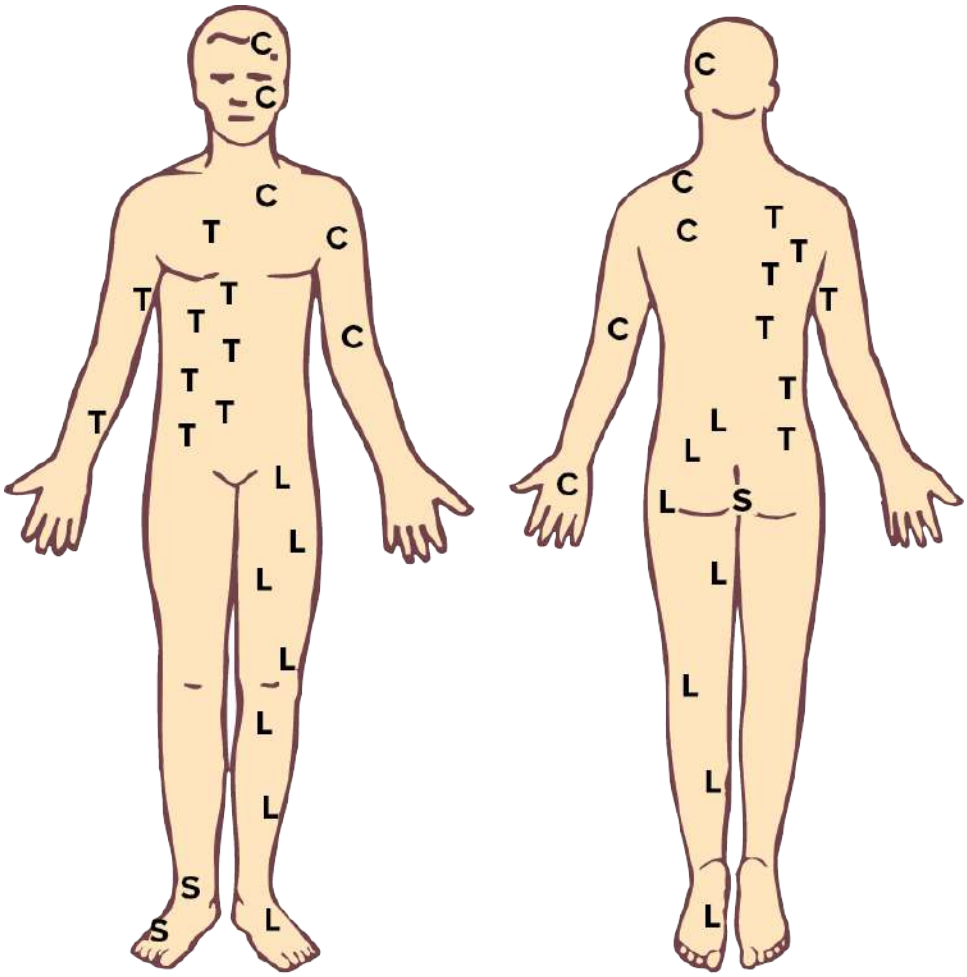
The medical profession tends to have a blind spot about various pain syndromes in the chest, especially the anterior chest and upper abdomen, caused by the common problem of dysfunction of the thoracic spine. Doctors who gain this insight are amazed at how often they diagnose the cause that previously did not enter their ‘programmed’ medical minds.

Physical therapy to the spine can be very effective when used appropriately. Unfortunately, many of us associate it with quackery. It is devastating for patients to create doubts in their minds about having a ‘heart problem’ or an ‘anxiety neurosis’ when the problem is spinal and it can be remedied simply (see CHAPTER 28).

Lumbar-sacral spinal dysfunction

The association between lumbar dysfunction and pain syndromes is generally easier to correlate. The pain is usually located in the low back and referred to the buttocks or the backs of the lower limbs. Pain manifestations of radiculopathy (sciatica) may follow dermatome patterns (see FIG. 55.1 in CHAPTER 55). Problems arise with referred pain to the pelvic area, groin and anterior aspects of the leg. Such patients may be diagnosed as suffering from inguinal or obturator hernial and nerve entrapment syndromes.

Typical examples of referral and radicular pain patterns from various segments of the spine are presented in FIGURE 15.3 .



C = cervical; T = thoracic; L = lumbar; S = sacral

FIGURE 15.3 Examples of referred and radicular pain patterns from the spine (one side shown for each segment)

Management of lumbar spinal dysfunction[5]

This is best managed conservatively under medical supervision with collaboration between the general practitioner and skilled physiotherapist. The patient should continue their normal activities even if uncomfortable, avoid painful aggravating activities and take basic analgesics, such as paracetamol and ibuprofen. Evidence supports the value of prescribed exercises and physical interventions such as traction and spinal mobilisation or manipulation for persistent pain (refer to CHAPTERS 27 and 28).

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Backache
- Exercises for your lower back
- Exercises for your neck
- Exercises for your thoracic spine
- Neck: painful neck
- Sciatica

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16 Urinary tract infection

Experience has taught them, as mine has me, that one must listen to reason and agree with Hippocrates, Galen, Avicenna and many others, ancient and modern, that there is no surer way to determine the temperaments and constitutions of people of either sex than to look at the urine.

DAVACH DE LA RIVIÈRE (18TH CENTURY), *THE MIRROR OF URINES*

Urinary tract infection (UTI) is a common problem affecting all ages and accounts for approximately 1% of all attendances in general practice. It is very common in sexually active women but uncommon in men and children.

Organisms causing UTI in the community are usually sensitive to most of the commonly used antibiotics. The most common pathogens are the bacteria *Escherichia coli* (*E. coli*), *Staphylococcus saprophyticus*, *Proteus*, *Klebsiella* and *Enterococcus* spp. Of great concern is the worldwide emergence of multidrug-resistant strains of *E. coli*. The important decision to make is whether to proceed with further investigation of the urinary tract. The morbidity of urinary infections in both children and adults is well known but it is vital to recognise the potential for progressive kidney damage, ending in chronic kidney failure. The main task in the prevention of chronic pyelonephritis is the early identification of patients with additional factors, such as reflux or obstruction, which could lead to progressive kidney damage.

UTI as a masquerade

UTI can be regarded as a masquerade when it presents with a constitutional problem or general symptoms, without symptoms suggestive of a urinary infection such as frequency, dysuria and loin pain. This applies particularly to infants and young children and the elderly but is not uncommon in adult women and in pregnancy. Acute UTI may occasionally present as acute abdominal pain. The causes of dysuria are outlined in the diagnostic strategy in CHAPTER 65 .

In infants and children, presenting non-specific symptoms include:

- fever
- lethargy and irritability
- poor feeding

- failure to thrive
- vomiting
- abdominal pain
- diarrhoea

In the elderly:

- confusion
- behaviour disturbance
- fever of undetermined origin

Key facts and checkpoints

- As always, a thorough examination of the patient presenting with urinary symptoms and their history is important.
- Screening of asymptomatic women has shown that about 5% have bacterial UTI.[1]
- About 1% of neonates and 1–2% of schoolgirls have asymptomatic bacteriuria.[2]
- About one-third of women have been estimated to have symptoms suggestive of cystitis at some stage of their life.
- The vast majority of these women have anatomically normal kidney tracts, are at no significant risk from the UTI and respond quickly to simple therapy. The prevalence of underlying abnormalities is estimated at around 4%.[3]
- UTIs are largely caused by organisms from the bowel that colonise the perineum and reach the bladder via the urethra. In many young women, infections are precipitated by sexual intercourse. Ascending infection accounts for 93% of UTIs.
- Haematogenous infection can occur sometimes, especially with the immunocompromised patient.
- Children with severe or recurrent UTIs require investigation for an underlying abnormality of the urinary tract.
- In the presence of a normal urinary tract there is no evidence that UTI leads to progressive kidney damage.

- Always consider any family history of urinary tract abnormalities.
- Infants less than 6 months old with a UTI have a significant risk of bacteraemia.
- Consider the NSAID tiaprofenic acid as a cause of non-infective cystitis.
- Cloudy or malodorous urine does not usually require investigation or treatment unless the person has other signs of a UTI.[2]
- Care should be exercised in deciding the need for dipstick urinalysis and microscopy, culture and sensitivity (MCU) tests in elderly patients including residential aged care facilities to ensure appropriate diagnosis and avoidance of unnecessary antibiotic use.[2]

Risk factors

- Female sex
- Sexual intercourse
- Diabetes mellitus
- Vesicoureteral reflux (VUR)
- Urinary tract obstruction/malformation/stricture
- Pregnancy
- Immunosuppression
- Menopause
- Diaphragm contraception or spermicidal exposure
- Instrumentation
- Bladder polyps, carcinoma, diverticula, stones
- Diverticulitis with colo-vesical fistula (?pneumaturia)

Classification and clinical syndromes

Sterile pyuria

This is defined as the presence of pus cells but a sterile urine culture.[2] The common causes of

sterile pyuria are:

- contamination of poorly collected urine specimens
- urinary infections being treated by antibiotics, i.e. inadequately treated infections
- genital infections (e.g. chlamydia urethritis)
- analgesic nephropathy
- staghorn calculi
- other kidney disorders (e.g. polycystic kidney)
- bladder tumours
- tuberculosis
- chemical cystitis (e.g. cytotoxic therapy)
- appendicitis

Asymptomatic bacteriuria[4]

This is defined as the presence of a significant growth of bacteria in the urine (concentration $>10^8$ colony forming units/L), which has not produced symptoms requiring consultation.[1]

Screening for and treatment of asymptomatic bacteriuria is not recommended except for:

- pregnant women because of the risk of pyelonephritis and pregnancy complications (see CHAPTER 100)
- patients before elective urological procedures (e.g. TURP)

Symptomatic bacteriuria

This is defined as the presence of frequency, dysuria and loin pain alone or in combination, together with a significant growth of organisms on urine culture.[2]

The clinical differentiation between cystitis or lower UTI and kidney or upper UTI cannot be made accurately on the basis of symptoms, except in those patients with well-defined loin pain and/or tenderness.

Acute cystitis (dysuria-frequency syndrome)[1]

- Inflammation of the bladder and/or urethra is associated with dysuria (pain or scalding with micturition) and/or urinary frequency.

- In severe cases, haematuria may be present, and the urine may have an offensive smell.
- Constitutional symptoms are minimal or absent.
- Other causes of dysuria and frequency include urethritis, prostatitis and vulvovaginitis, all of which can normally be distinguished clinically.

Acute pyelonephritis[1]

- Acute bacterial infection of the kidney produces loin pain and constitutional upset, with fever, rigors, nausea and sometimes vomiting.
- The symptoms of acute cystitis are often also present.
- The differential diagnosis includes causes of the acute abdomen, such as appendicitis, cholecystitis and acute tubal or ovarian diseases. The presence of pyuria and absence of rebound tenderness are helpful in distinction.

The clinical manifestations of UTI are summarised in FIGURE 16.1 .

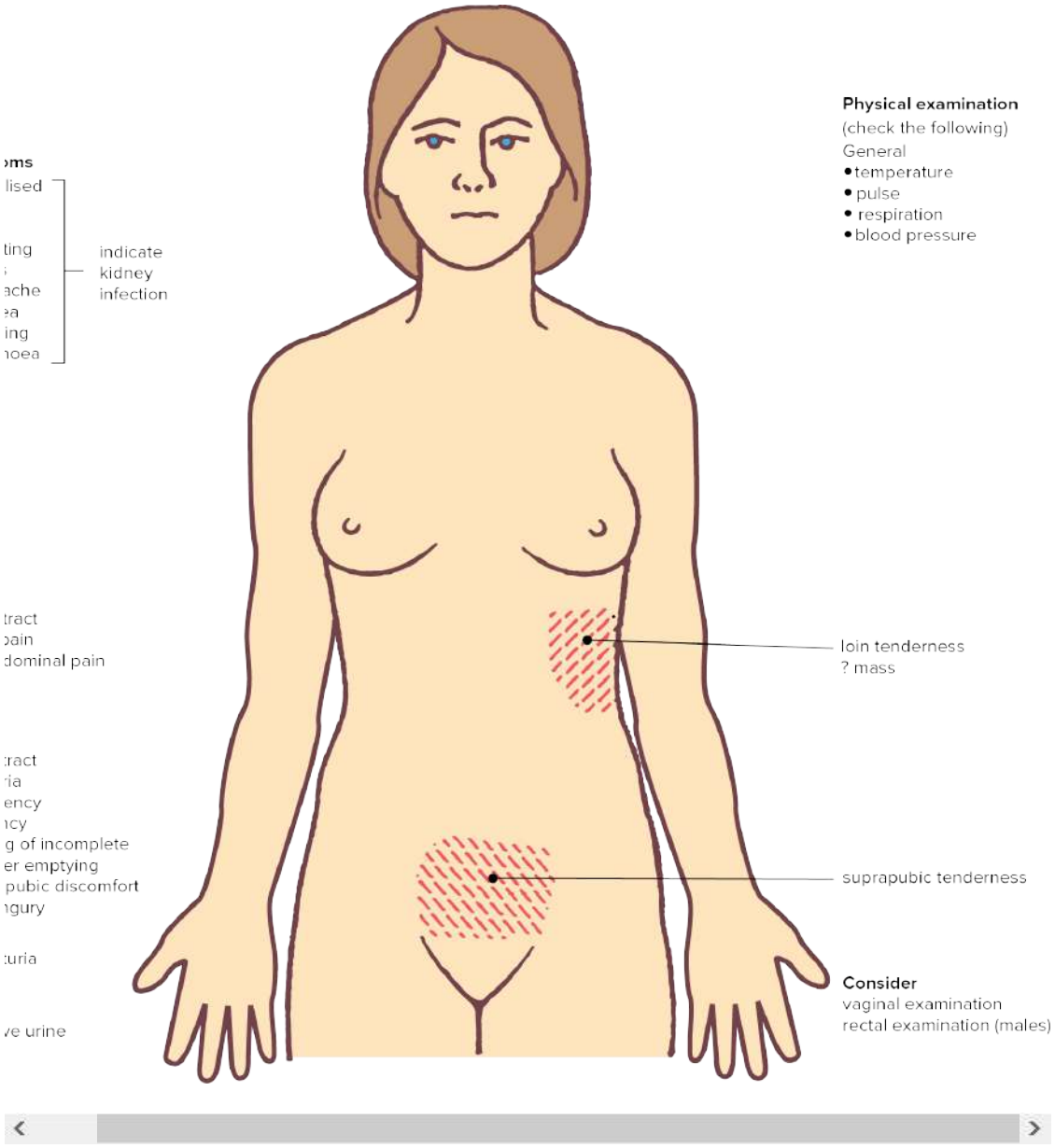

FIGURE 16.1 Clinical manifestations of urinary tract infection

Uncomplicated urinary tract infection

This is cystitis occurring in the uninstrumented non-pregnant female without structural or neurological abnormalities. Acute infection is most commonly caused by *E. coli* and *Staphylococcus saprophyticus*.

Complicated urinary tract infection[5]

This is associated with anatomical or functional abnormalities (e.g. diabetes, urinary

calculi) that increase the risk of serious complications or treatment failure.

Urethral syndrome

The urethral syndrome (sometimes termed abacterial cystitis) is where the patient presents with dysuria and frequency and even abdominal pain but does not show a positive urine culture.[3]

- 30–40% of adult women with urinary symptoms have this syndrome.[3]
- Many actually have bacterial cystitis but a negative culture.
- The organisms may be anaerobic or fastidious in their culture requirements.
- The organisms may include *Ureaplasma*, *Mycoplasma genitalium*, *Chlamydia* and viruses.
- The urine may have antiseptic contamination or residual antibiotic.
- The infection may be undergoing spontaneous resolution at the time of the culture.

Interstitial cystitis[3]

This is an uncommon but important cause of the urethral syndrome.

- The classic symptoms are frequency day and night and a dull suprapubic ache relieved briefly by bladder emptying.
- The feature is small haemorrhages on distension of the bladder.
- Treatment is hydrodistension ± a course of tricyclics, for example amitriptyline.

Laboratory diagnosis

The laboratory diagnosis of UTI depends on careful collection, examination and culture of urine. This is recommended for the people listed in TABLE 16.1 . It is not mandatory for non-pregnant women with suspected cystitis when empirical treatment may be appropriate.

Collection of urine[1]

It is best to collect the first urine passed in the morning, when it is highly concentrated and any bacteria have been incubated in the bladder overnight. Preferably the urine should be taken to the laboratory immediately, but it can be stored for up to 24 hours at 4°C to prevent bacterial multiplication.

- *Clean catch midstream specimen of urine (MSU).* This is best collected from a full bladder, to allow at least 100 mL of urine to be passed before collection of the MSU. It is important that the urine flow is continuous, and the container is moved in and out of the stream collecting at

least 20 mL.

In women, consider cleaning the genital area first (preferably with a sterile wipe). Sit on the toilet and swing one knee to the side as far as possible. The labia are then held apart with the fingers of one hand to prevent contact with the urinary stream while the specimen is collected after passing a small amount of urine into the toilet.

In males, the foreskin (if present) is retracted and the glans washed with clean water.

In children, a midstream clean catch (MCC) is useful (although prone to contamination) especially in the hands of experienced collectors. The parent holds the child over a sterile bowl placed under cleansed genitalia.

In infants, the three-person French technique is useful. This is where the child is held in a 'frog leg' position or with arms and legs dangling. Another person holds a sterile urine container to catch the urine. A trained person stimulates the bladder by tapping over it at 100 light taps per minute for 30 seconds then massages the paravertebral area for up to 3 minutes or until voiding.

- *Catheter specimen of urine (CSU).* In women who have difficulty with collecting an uncontaminated MSU (as is commonly the case in the elderly, the infirm and the grossly obese), a short open-ended catheter can be inserted and a specimen collected after 200 mL has flushed the catheter.

- *Suprapubic aspirate of urine (SPA).* This is an extremely reliable way to detect bacteriuria in neonates and in patients where UTI is suspected but cannot be confirmed because of low colony counts or contamination in an MSU. Under topical anaesthesia, a needle (lumbar puncture needle in adults) is inserted into the very full bladder about 1–2 cm above the pubic symphysis, and 20 mL is collected by a syringe. Any organisms in an SPA specimen indicate UTI (see FIG. 16.2).

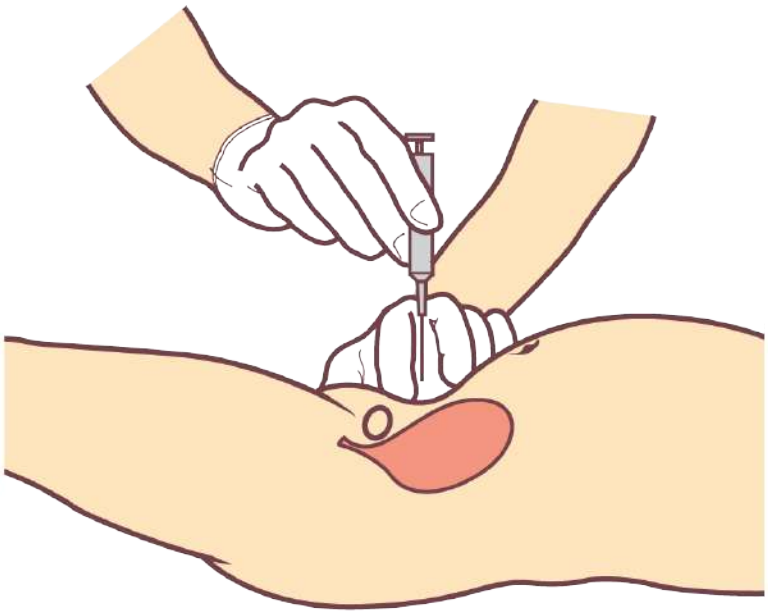

FIGURE 16.2 Suprapubic aspiration of urine in a child

Urine specimen collection in children

All children with a UTI require a urine specimen. It is diagnosed by significant growth on MSU, CSU, MCC or SPA.

- Bag specimen: cannot diagnose UTI
- MSU—usually by 3–4 years when cooperative
- MCC—practical and reliable
- SPA—reliable and the best option
- CSU—for failed SPA or those unable to void on request

Dipstick testing

Dipstick findings of urinary leucocytes or nitrite are suggestive of UTI and may be an indication for empirical treatment if symptomatic. The reagents in dipstick testing are generally sensitive but have to be interpreted with care. Leucocyte esterase dipsticks are useful in detecting pyuria and give a good guide to infection with a specificity of 94–98% (2–6% false positive) and 74–96% sensitivity (4–26% false negatives).[6] Positive nitrite dipsticks give a useful guide to the presence of bacteria. Unexplained haematuria detected by dipstick analysis needs investigation.

Microscopic examination

The urine is examined under a microscope to detect pyuria (more than 10 pus cells—WBCs—per high-powered field) but should be examined in a counting chamber to calculate the number of WBCs/mL of urine. In the counting chamber pyuria is >8000 WBC/mL in phase-contrast microscopy. Pyuria is a very sensitive sign of UTI.

Vaginal squames and debris indicate contamination.

Culture of the urine

The nature and number of organisms present in the urine are the most useful indicators of UTI.[1]

- Most common are enteric organisms. *E. coli* (especially) and *Staphylococcus saprophyticus* are responsible for over 90% of UTIs, with other Gram-negative organisms (*Klebsiella* sp. and *Proteus* sp.), *Enterococcus* sp. and Gram-positive cocci (*Streptococcus faecalis* and other staphylococci) also responsible.
- Infections due to organisms other than *E. coli* (e.g. *Pseudomonas sp*.) are suggestive of an underlying kidney tract abnormality.
- If $>10^5$ colony forming units (cfu) per mL of bacteria are present in an MSU, it is highly likely that the patient has a UTI.
- On the other hand, it is most important to realise that up to 30% of women with acute bacterial cystitis have less than 10^5 cfu/mL in the MSU. For this reason, it is reasonable to treat women with dysuria and frequency even if they have $<10^5$ cfu/mL of organisms in an MSU.

Summary: MCU (microscopy and culture urine)

Significant levels for UTI:

- Microscopy: WBC >10 per mL (10×10^6/L)
- Culture: counts $>10^5$ cfu/mL (10^8/L)

Other investigations

- FBE, ESR/CRP, blood culture (if febrile and unwell), consider U&E, PSA (men)

Acute uncomplicated cystitis

Advice to women (especially if recurrent attacks):

- Keep yourself rested.
- Drink a lot of fluid: 2–3 cups of water at first and then 1 cup every 30 minutes.
- Try to empty your bladder completely each time.
- Use analgesics such as paracetamol for pain.
- Make the urine alkaline by taking sodium citrotartrate (4 g orally 6 hourly)—not if taking nitrofurantoin.

UTI: basic management

- Urine dipstick
- Urine microscopy and culture
- First-line antibiotics—trimethoprim or cephalexin
- Alkaliniser for severe dysuria
- High fluid intake
- Check sensitivity—leave or change ABs

Consider further investigation (see TABLE 16.1)

Table 16.1 Investigation of symptomatic urinary tract infections

Investigations are indicated in:

All children

All males

All women with:

- acute pyelonephritis
- recurrent infections: >2 per year
- confirmed sterile pyuria
- other features of kidney disease, e.g. haematuria
- pregnancy

Others:

- with failed antibiotic treatment
- with recent international travel

Basic investigations include:

MCU—microscopy and culture
Kidney function tests: plasma urea and creatinine, eGFR
Intravenous urogram (IVU) and/or ultrasound

Special considerations:

In children: micturating cystourethrogram (MCUG), nuclear scans (DMSA, MAG3)
In adult males: consider prostatic infection studies if IVU normal
In severe pyelonephritis: ultrasound or IVU (urgent) to exclude obstruction
In pregnant women: ultrasound to exclude obstruction

Treatment (non-pregnant women)[3,7]

Use for 10 days in women with known urinary tract abnormality:

- trimethoprim 300 mg (o) daily for 3 days (first choice)

  or

- cephalexin 500 mg (o) 12 hourly for 5 days

  or

- amoxicillin + clavulanate 500/125 mg (o) 12 hourly for 5 days

  or

- nitrofurantoin 100 mg (o) 6 hourly for 5 days

  or

- norfloxacin 400 mg (o) 12 hourly for 3 days (if resistance to above agents proven and if susceptible, Caution about tendinopathy and tendon rupture.)

  No follow-up is required if women remain asymptomatic after treatment.

Note:

- Avoid using important quinolones—norfloxacin or ciprofloxacin—as first-line agents.
- Cotrimoxazole is not first line because it has no advantage over trimethoprim and has more side effects.
- Treatment failures are usually due to a resistant organism or an underlying

abnormality of the urinary tract.

Pregnant women[8,9]

UTI in pregnant women requires careful surveillance. Asymptomatic bacteriuria should always be excluded during early pregnancy because it tends to be blown into a full infection. Treat asymptomatic bacteriuria in pregnancy as for acute cystitis.

Treatment of acute cystitis (empirical):

- cephalexin 500 mg (o) 12 hourly for 5 days

  or

- nitrofurantoin 100 mg (o) 6 hourly for 5 days

  or

- amoxicillin + clavulanate 500/125 mg (o) 12 hourly for 5 days

Repeat MCU 1--2 weeks after completion.

Adult males[7]

Consider the cause (see risk factors above).

Investigations: MCU, U&E, ultrasound.

Treatment (empirical, while awaiting investigation):

- trimethoprim 300 mg (o) daily for 7 days

  or

- cephalexin 500 mg (o) 12 hourly for 7 days

  or

- amoxicillin + clavulanate 500/125 mg (o) 12 hourly for 7 days

  or

- nitrofurantoin 100 mg (o) 6 hourly for 7 days

  or

- norfloxacin 400mg (o) 12 hourly for 7 days

Note: All males with a UTI should be investigated to exclude an underlying abnormality, e.g.

prostatitis, obstruction.

Acute pyelonephritis[10]

Urine microscopy and culture is mandatory. Mild cases can be treated with oral therapy alone for a longer duration than the recommended course for uncomplicated cystitis. For empirical therapy, use amoxicillin/clavulanate (875/125 mg (o) 12 hourly) for 10–14 days or ciprofloxacin (500 mg (o) 12 hourly) for 7 days. Modify empirical therapy based on culture and susceptibility results.

For severe infection with suspected septicaemia, admit to hospital and treat initially with parenteral antibiotics after taking urine for microscopy and culture, and blood for culture. It is a particular problem if acquired in pregnancy.

- amoxicillin/ampicillin 2g IV 6 hourly

plus

- gentamicin 4–6 mg/kg/day, single daily IV dose

Follow with oral therapy for a total of 14 days.

Drug levels of gentamicin require monitoring. Gentamicin can be replaced with IV cefotaxime or ceftriaxone.

Consider investigation for an underlying urinary tract abnormality, especially in men and in patients that remain unwell after 72 hours of treatment.

Recurrent or chronic urinary tract infections[11,12]

Recurrent infections occur as a relapse of a previously treated infection or because of re-infection, often with differing organisms. Persistent (chronic) UTIs indicate that the organism is resistant to the antimicrobial agents employed or that there is an underlying abnormality such as a kidney stone or a chronically infected prostate in the male patient. MCU is mandatory. Such infections may be treated with prolonged courses of an appropriate antibiotic or removal of the focus of infection.[13]

In men and children, an anatomical abnormality is usual, while recurrent cystitis in women often occurs despite a normal tract.

Treatment[14]

Treat an acute episode of recurrent UTI as for cystitis or pyelonephritis

Prevention including antibiotic prophylaxis[14]

In some female patients with recurrent UTI a single dose of a suitable agent within 2 hours after