39 Surgical site infection and antimicrobial prophylaxis

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Key points

- Surgical site infection is a major cause of mortality and morbidity.
- Development of surgical site infection is a complex process influenced by host, operative and microbial factors.
- The microbial cause of surgical site infection varies with type of procedure but *Staphylococcus aureus* remains the most commonly implicated pathogen.
- Surveillance of surgical site infection is necessary to benchmark and improve prevention strategies.
- Antimicrobial prophylaxis is just one of many approaches to reduce surgical site infection.
- Not all operations require antimicrobial prophylaxis.
- Antimicrobial prophylaxis should be used only where there is evidence of efficacy or expert consensus that benefits outweigh risks.
- The choice of antimicrobial prophylaxis depends on the operation, pharmacokinetics, pharmacodynamics and patient factors.
- The timing of antimicrobial administration is key to reducing surgical site infection.
- Pharmacists are unlikely to see many patients before surgery; they must therefore develop systems to ensure that appropriate antimicrobial prophylaxis is given at the right time.

Surgery is the branch of medical science that treats injury or disease or improves bodily function through operative procedures. Surgery has been used for thousands of years but has always been complicated to some extent by infection. Currently, surgery is an integral part of the management of many medical conditions and remains the definitive treatment for many cancers. Infections developing at the site of invasive surgical procedures are frequently referred to as surgical site infections. Surgical site infections occur when pathogenic micro-organisms contaminate a surgical wound, multiply and cause tissue damage. The term 'surgical site infection' encompasses not only infection at the site of incision but also infections of implants, prosthetic devices and adjacent tissues involved in the operation.

Epidemiology

In England, there are over nine million operations and interventions undertaken each year. Over 50% of these are performed as day cases and many patients are admitted on the day of surgery (Health and Social Care Information Centre, 2009). Healthcare-associated infections (HCAIs), including surgical site infections, complicate around 7% of all hospital admissions (HIS/ICNA, 2007). Surgical site infections are of major clinical importance because they account for 14–16% of all healthcare-associated infections (HPS, 2009; Public Accounts Committee, 2009) and are associated with considerable morbidity and mortality. One-third of peri-operative deaths are related to surgical site infections (Astagneau et al., 2001). It has been estimated that surgical site infections double the length of hospital stay (Coello et al., 2005). While surgical site infections can be common in some procedures, the incidence can be minimised by the care provided before and after the operation, together with the skill of the surgeon (HPS, 2009).

Surveillance

Monitoring the incidence of surgical site infections is hampered by the lack of agreed measuring systems. In particular, to monitor the rates of surgical site infection within an organisation, or to benchmark between organisations, there needs to be a standard approach to diagnosis. Criteria for such a definition have been developed by the Centres for Disease Control and Prevention (CDC) (Mangram et al., 1999) and these are presented in Table 39.1. More detailed surgical site infection scoring systems have been developed but these are time consuming to use.

Mandatory surveillance for surgical site infections in orthopaedic surgery in the UK was introduced in 2003. In addition, Scotland monitors most other common procedures (http://www.hps.scot.nhs.uk) while in Wales caesarian section is also monitored (http://www.wales.nhs.uk). England has a voluntary reporting system for a broader range of operations (http://www.hpa.org.uk). All report their findings annually. Many surgical site infections, for example, those involving

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Table 39.1 Criteria for defining surgical site infection (Mangram et al., 1999)

Type	Level	Signs and symptoms
Superficial incisional	Skin and subcutaneous tissue	Localised (Celsian) signs such as redness, pain, heat or swelling at the site of the incision or by the presence of pus within 30 days
Deep incisional	Fascial and muscle layers	Presence of pus or an abscess, fever with tenderness of the wound, or a separation of the edges of the incision exposing the deeper tissues within 30 days (or 1 year if an implant used)
Organ or space infection	Any part of the anatomy other than the incision that is opened or manipulated during the surgical procedure, for example, joint or peritoneum	Loss of function of a joint, abscess in an organ, localised peritonitis or collection. Ultrasound or CT scans confirm infection. Within 30 days (or 1 year if implant is used)

prosthetic joints, often develop late (>28 days post-operation), so post-discharge surveillance schemes are essential. Patients need to be aware how a surgical site infection may present after discharge from hospital. Surveillance of surgical site infections and feedback to the surgical team has been shown to reduce rates of infection (Gastmeier et al., 2005).

Risk factors

Surgical site infections can be categorised into three groups: superficial incisional, deep incisional and organ or space (Fig. 39.1) Whether a wound infection occurs after surgery depends on a complex interaction between the following:

- Procedure-related factors, for example, implantation of foreign bodies, degree of trauma to host tissues and experience of surgeon

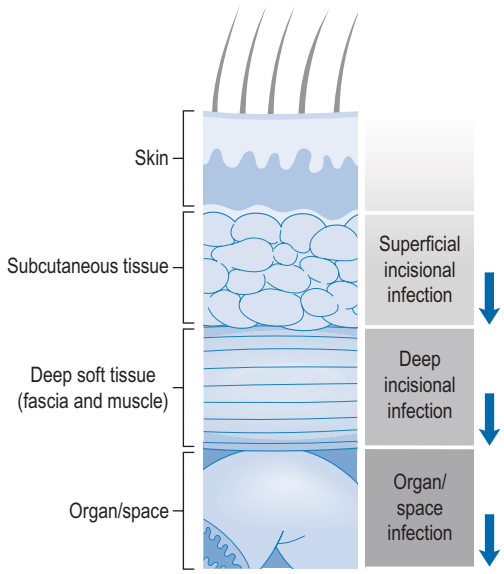


Fig. 39.1 Schematic representation of the anatomical classification of surgical site infection (Horan et al., 1992). Reproduced with permission from the University of Chicago Press.

- Patient related factors, for example, host immunity, nutritional status and the presence or absence of diabetes
- Microbial factors (tissue adherence and invasion)
- Peri-operative antimicrobial prophylaxis.

A system to stratify operative wounds by the expected level of bacterial contamination (Table 39.2) was developed to help predict likely infection rates (Mangram et al., 1999). A number of other factors have also been found to affect the incidence of surgical site infection and are discussed below.

Prosthetic implants

Medical implants have a detrimental effect on host defences such that a lower bacterial count is needed to initiate infection. Hence, there is a greater risk of infection during implant surgery. Bacteria growing on an abiotic surface, such as a prosthetic hip implant or heart valve, together with a protective layer of microbial polymers are known as a biofilm (Donlan and Costerton, 2002). Antimicrobials are frequently ineffective against micro-organisms growing in biofilms, making treatment of implant infections problematic and their prevention even more important.

Duration of surgery

The longer the operation, the greater is the risk of wound infection. This, in turn, may be influenced by the experience (Fig. 39.2) speed and skill of the surgeon and is additional to the classification of the operation by risk of infection, for example, clean, contaminated, dirty or infected.

Patient related factors

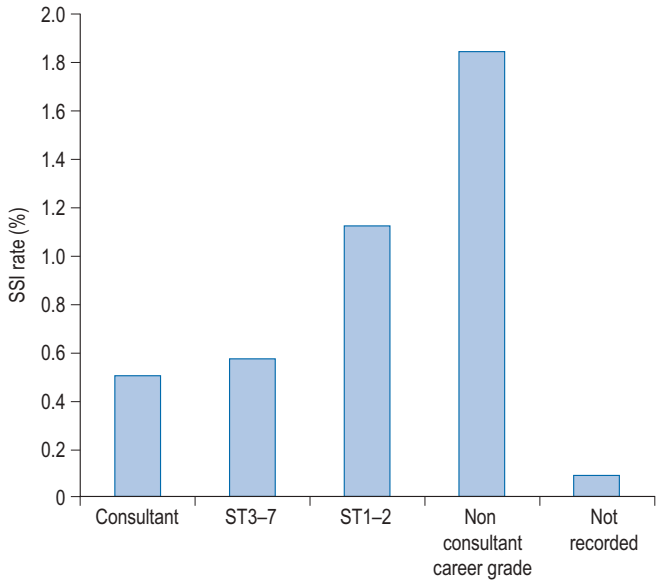
A number of patient related factors are known to influence the likelihood of developing a surgical site infection and include the following:

- Wound potential for infection, for example, clean, contaminated, dirty or infected site
- Physical status of patient (Table 39.3)
- Duration of procedure.

Table 39.2 Classification of surgical procedures by risk of infection (Mangram et al., 1999)

Type of procedure	Definition	Wound infection rate (%)	Example	Need for prophylaxis
Clean	Atraumatic; no inflammation encountered, no break in technique; gastro-intestinal, genitourinary and respiratory tracts not entered	1.5–4.2	Inguinal hernia repair	Not usually required
Contaminated	Gastro-intestinal or respiratory tract entered but without spillage; oropharynx, appendectomy, sterile genitourinary or biliary tract entered; minor break in technique	<10	Cholecystectomy (no spillage)	Usually required
Clean-contaminated	Acute inflammation; infected bile or urine; gross spillage from gastro-intestinal tract; major lapse in technique; fresh traumatic wound (12–24 h)	10–20	Appendicectomy	Required
Dirty and infected	Established infection; transection of clean tissues to enable collection of pus; traumatic wound with retained devitalised tissue; faecal contamination; delayed treatment	20–40	Sigmoid colectomy (Hartmann's procedure) for faecal peritonitis	Treatment required (not prophylaxis)

For each surgical procedure, a score of 0–3 is allocated to represent the number of risk factors present. Patients with a score of 0 are at the lowest risk of developing a surgical site infection, while those with a score of 3 have the greatest risk (Table 39.4). Use of this risk index allows comparison of similar patient groups in terms of surgical site infection risk over time. The risk index is a significantly better predictor of surgical-wound risk than the traditional wound classification system and performs well across a broad range of operative procedures.



ST = Speciality registrar grade, number represents years of training

Fig. 39.2 Surgical site infection rate by grade of operator for orthopaedic surgery 2008 (Health Protection Scotland, 2009). Reproduced with kind permission from Health Protection Scotland.

Other factors

There are a number of other risk factors that may increase the risk of a surgical site infection (Table 39.5) for an individual patient but the impact has not been quantified to the extent of those risk factors discussed above.

Table 39.3 American Society of Anesthesiology (ASA) classification of physical status (Mangram et al., 1999)

ASA score	Physical status
1	A normal healthy patient
2	A patient with mild systemic disease
3	A patient with a severe systemic disease that limits activity but is not incapacitating
4	A patient with an incapacitating systemic disease that is a constant threat to life
5	A moribund patient that is not expected to survive 24 h with or without operation

Table 39.4 Risk index based on presence of co-morbidity and duration of operation (Culver et al., 1991)

Risk index	Infection rate (%)
0	1.5
1	2.9
2	6.8
3	13.0

Table 39.5 Patient and operative risk factors for surgical site infection

Patient risk factors	Operative risk factors
Advanced age	Tissue ischaemia
Malnutrition	Lack of haemostasis
Obesity	Tissue damage, for example, crushing by surgical instruments
Concurrent infection	Presence of necrotic tissue
Diabetes mellitus	Presence of foreign bodies including surgical materials
Liver impairment	
Renal impairment	
Immune deficiency states	
Prolonged preoperative stay	
Blood transfusion	
Smoking	

Smoking

Smoking increases the risk of developing a wound infection (Myles et al., 2002). The mechanism is not known but tobacco use may delay wound healing via the vasoconstricting effects of nicotine and thus increase the risk of infection (Myles et al., 2002).

Diabetes mellitus

Long-term diabetes does not appear to have any impact on the risk of developing a surgical site infection. However, perioperative fluctuations in blood glucose for up to 48 h have been shown to double the infection risk in cardiac patients (Latham et al., 2001).

Age

Increasing age is associated with an increased risk of surgical site infection. However, there is debate whether age serves simply as a marker for underlying disease or whether the decline in immune function with age is the significant factor. A study of 72,000 patients in the USA, which adjusted for hospital type, procedure, duration, wound class and physical status of the patient, showed a 1.1% increase in surgical site infection per year of age from the age of 18 to 65 years, but a 1.2% decrease in individuals over 65 years (Kaye et al., 2005). In contrast, the findings of the English surgical site infection surveillance scheme (Fig. 39.3) indicated that the chance of getting a surgical site infection were 37% higher for a 65-year-old person compared to a 45-year-old person (HPA, 2008).

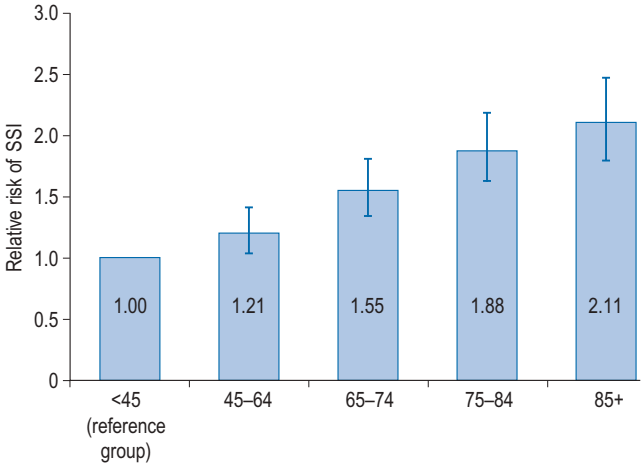


Fig. 39.3 Relative risk of surgical site infection by age group, 2003–2007, adjusted for surgical category (reference age group <45 years) (HPA, 2008). Reproduced with kind permission from Health Protection Agency.

Pathogenesis

Most surgery involves an incision through one of the body's protective barriers, typically the skin or other epithelial surface such as the conjunctiva or tympanic membrane. When intact, these provide an excellent barrier to entry of both exogenous and endogenous bacteria into other epithelial surfaces including the mucosal surfaces of the gastro-intestinal and genitourinary tracts, which, when intact, prevent entry of the luminal contents into the surrounding tissues and organs.

Any surgical operation will breach at least one of the surfaces mentioned and allow entry of bacteria. Whether an infection follows depends on the ability of other defences to kill the invading bacteria. Important host mechanisms include antibodies, complement and phagocytes.

Development of a surgical site infection depends on survival of the contaminating micro-organism in a wound site at the end of a surgical procedure; the pathogenicity and number of these micro-organisms; and the host's immune response. Most micro-organisms are from the host (endogenous), but are occasionally introduced via surgical instruments, the environment or contaminated implants (exogenous). The likely invading micro-organism varies according to the type of surgery (Table 39.6). Data for

Table 39.6 Likely pathogens in post-operative wound infections

Category of surgery	Most likely pathogen(s)
Clean	
Cardiac/vascular/orthopaedic	Coagulase-negative staphylococci, *S. aureus*, Gram-negative bacilli
Breast	*S. aureus*
Clean-contaminated	
Burns	*S. aureus, Pseudomonas aeruginosa*
Head and neck	*S. aureus, Streptococcus* spp., anaerobes (from oral cavity)
Gastro-intestinal tract	Coliforms, anaerobes *(Bacteroides fragilis)*
Urogenital tract	Coliforms, *Enterococcus* spp.
Dirty	
Ruptured viscera	Coliforms, anaerobes (*B. fragilis*) *S. aureus*
Traumatic wound	*Streptococcus pyogenes, Clostridium* spp.

England from 2003 to 2007 has shown that the predominant organism was *Staphylococcus aureus*, which accounted for 38% of all surgical site infections (Fig. 39.4); 64% of these were caused by a meticillin-resistant strain (MRSA). The proportion of surgical site infections caused by *S. aureus* was highest in hip hemiarthroplasty (57%), followed by limb amputation (54%) and open reduction of long bone fracture (52%). *Enterobacteriaceae* (coliforms) caused the second largest group of infections, accounting for 21% of all surgical site infections. These were the prominent causes of surgical site infections in three categories: large bowel surgery (33%), coronary artery bypass graft (32%) and small bowel surgery (30%).

Although there was a significant reduction in the risk of a surgical site infection for all categories over the 5 year period monitored, there was no change in the proportion of *S. aureus,* infections that were due to MRSA. Infection control measures including the introduction of mandatory MRSA screening for elective patients in 2009 should improve this. Known or previous MRSA carriers can be 'decolonised' and appropriate prophylactic antimicrobials administered that cover MRSA (e.g. teicoplanin).

Prevention of surgical site infection

The evidence that supports interventions to minimise surgical site infection has been highlighted in national guidelines (NICE, 2008a) and categorised into four areas: information to patients, preoperative phase, peri-operative phase and post-operative phase (Table 39.7). When selecting antimicrobial prophylaxis regimens or evaluating potential prophylaxis failures, it is important to ensure that all four aspects of prevention have been addressed.

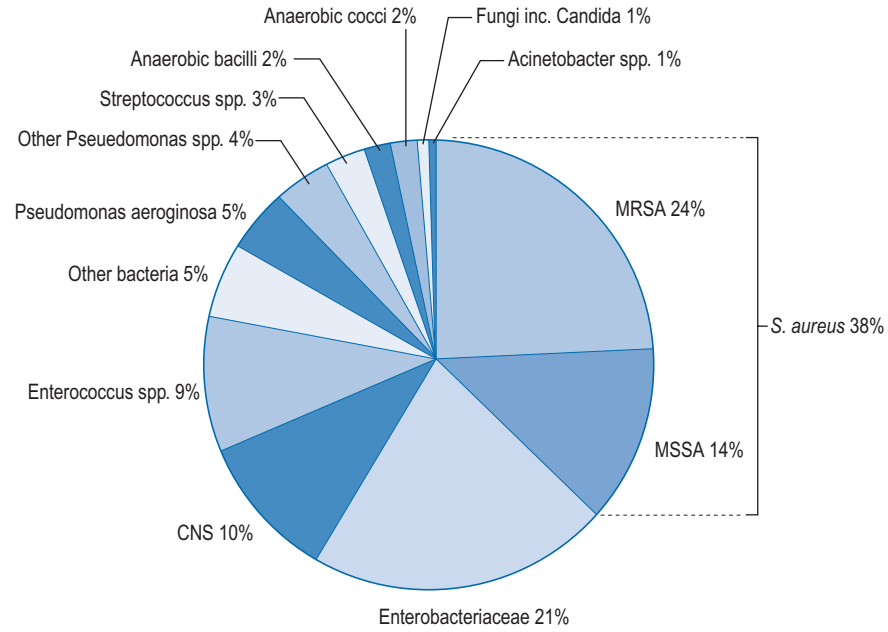


Fig. 39.4 Surgical site infection isolated organisms 2003–2007 (HPA, 2008).

Table 39.7 Recommendations for the prevention and treatment of surgical site infections (NICE, 2008a)

Category	Recommendation
Information for patients and carers	How to recognise a surgical site infection and what to do
Preoperative phase	Patient preparation: pre-op washing, hair removal, nasal MRSA decontamination and bowel preparation Antimicrobial prophylaxis guidance Staff preparation and theatre movement
Intra-operative phase	Operating team preparation Patient skin preparation Maintaining patient homeostasis Wound dressings
Post-operative phase	Dressing and cleansing the wound Antimicrobial treatment for surgical site infection Debridement of surgical site infections

Antimicrobial prophylaxis

In the early 1960s, it was demonstrated, using a guinea-pig model, that surgical-wound infection could be reduced by administration of an antimicrobial just before an incision was made, but the beneficial effect disappeared if antimicrobial administration was delayed by 3–4 h after the incision (Burke, 1961). Since then, many clinical trials have indicated the benefit of maintaining adequate antimicrobial tissue levels from the time of initial surgical incision until closure.

There are potential adverse consequences to the administration of antimicrobials for both the individual and the population. For the individual, side effects, ranging from antimicrobial associated diarrhoea or thrush to life-threatening allergic reactions, may arise. From the population perspective, the development of antimicrobial resistant bacteria is a concern. Antimicrobial prophylaxis should, therefore, only be offered to patients where there is evidence or, in the absence of evidence, expert consensus that the potential benefits of prophylaxis outweigh the risks.

The number of patients that need to be treated with antimicrobial agents to prevent one infection in the different types of surgery are presented in Table 39.8.

The infection risk associated with a particular surgical procedure and evidence of efficacy should be used to determine whether antimicrobial prophylaxis is to be administered. Not all surgical procedures warrant antimicrobial prophylaxis.

Choice of antimicrobial

Once it has been determined that antimicrobial prophylaxis is required, the next step is to select an appropriate agent(s). The choice of antimicrobial should take into account the following:

- Likely infecting organisms (procedure specific)
- Local susceptibility of potential pathogens to antimicrobials
- Pharmacokinetics, for example, penetration of antimicrobial to the site(s) in question
- Patient allergy to penicillins or other antimicrobials
- Administration time (bolus better than infusion)
- Drug cost
- Carriage of resistant organisms, for example, methicillin-resistant *S. aureus* (MRSA)
- Prevalence of *Clostridium difficile* infection in the hospital.

The majority of clinical trials that have demonstrated the benefit of antimicrobial prophylaxis are outdated, and probably do not reflect current surgical practice. First and second generation cephalosporins (cefazolin and cefuroxime) have been the mainstay of agents studied (Bratzler and Houck, 2004). There are advantages and disadvantages with using cephalosporins. The advantages include a low anaphylaxis risk, but they have the disadvantage of excessive or inadequate spectrum of cover depending on the operation (Morgan, 2006) and a strong association with *Clostridium difficile* infection. Many antimicrobials used in prophylaxis have not been extensively studied in clinical trials, but are selected on a theoretical basis of their antimicrobial spectrum (see Tables 39.9–39.11).

Table 39.8 Example of number needed to treat (NNT) for antimicrobial prophylaxis (SIGN, 2008)

Type of surgery	Operation	NNT	Outcome
Upper GI surgery	Stomach and duodenal surgery	5	Wound infection
Lower GI surgery	Colorectal surgery	4	Wound infection and intra-abdominal abscesses
Gynaecological	Caesarian section	19	Wound infection
Orthopaedic	Arthroplasty (hip replacement)	42	Hip infection

NNT is the number of patients that need to be treated to prevent one infection compared to receiving no antimicrobials.

Table 39.9 Antimicrobial susceptibility of common pathogens (adapted from SIGN, 2008)

Surgical site infection for a skin wound at any site	
S. aureus	Highly variable (30–60% susceptible) to flucloxacillin therefore MRSA screening essential
Beta haemolytic Streptococci (BHS)	90% susceptible to penicillins, macrolides or clindamycin
Additional pathogens by site of infection	
Head and neck surgery	
Oral anaerobes	95% susceptible to metronidazole or co-amoxiclav
Operations below the diaphragm	
Anaerobes	95% susceptible to metronidazole or co-amoxiclav
E. coli and other Enterobacteriaceae	80–90% of *E. coli* sensitive to cefuroxime, co-amoxiclav (or other β-lactam with inhibitor combination) or gentamicin
Insertion of a prosthesis, graft or shunt	
Coagulase-negative Staph (CNS)	Two-thirds of CNS are methicillin-resistant, but β-lactams may still be used but preferably with a second agent with staphylococcal cover, for example, gentamicin, or a glycopeptide used instead. See above for *S. aureus*.
S. aureus, diphtheroids	

Timing and duration

Timing of antimicrobial administration is one of the most important aspects of prophylaxis regimens. Animal studies and latterly clinical observational studies have shown that prophylaxis is most effective when given immediately before an operation (within 30 min of induction of anaesthesia), so that antimicrobial activity is present for the duration of the operation and for about 4 h afterwards. Antimicrobials given too early prior to surgery are associated with prophylaxis failure, presumably because serum and tissue levels are not sustained during the surgical procedure. Similarly, for each hour antimicrobial administration was delayed after the start of the operation there was an increased rate of wound infection. This suggests bacterial replication, once commenced, cannot be eliminated by antimicrobial regimens designed for prophylaxis. The microbiological basis for these observations is likely to be that bacterial reproduction at a logarithmic rate follows a lag phase of relatively little increase in bacterial population. The lag phase for wound infection bacteria lasts typically 3–4 h. If bacteria inoculated into a wound can be killed or inhibited by antimicrobials given early, the immune system can kill the remaining organisms. However, if antimicrobials are given only when the growth curve has entered the logarithmic phase, the chances of successful prophylaxis are reduced.

Formerly, protocols for prophylaxis extended for several post-operative days. Now, single dose schedules are increasingly common with greater emphasis on ensuring immediate preoperative administration. As surgery may

Table 39.10 Micro-organisms commonly isolated from surgical site infections and prophylactic antimicrobials used in common surgical procedures (Prtak and Ridgway, 2009)

Surgical procedure	Most common micro-organisms	Examples of prophylactic IV antimicrobials
Gastro-intestinal	Bowel flora	
• Upper gastro-intestinal tract	*S. aureus*, Gram-negative bacilli	Co-amoxiclav or cefuroxime or gentamicin
• Biliary	*S. aureus*, Gram-negative bacilli (enterococci, anaerobes)	Co-amoxiclav or cefuroxime and metronidazole or gentamicin and metronidazole
• Colorectal/appendicectomy	*S. aureus*, Gram-negative bacilli, anaerobes	Co-amoxiclav or cefuroxime and metronidazole or gentamicin and metronidazole
Urogenital		
• Transrectal biopsy	*S. aureus*, Gram-negative bacilli, anaerobes	Co-amoxiclav or cefuroxime and metronidazole or gentamicin and metronidazole
• Transurethral resection of prostate	*S. aureus*, Gram-negative bacilli, enterococci	Co-amoxiclav or cefuroxime or gentamicin
Obstetric/gynaecological		
• Caesarean section	*S. aureus*, Gram-negative bacilli, streptococci (anaerobes)	Co-amoxiclav or cefuroxime and metronidazole
• Hysterectomy	*S. aureus*, Gram-negative bacilli, anaerobes	Co-amoxiclav or cefuroxime and metronidazole
Vascular		
• Reconstructive arterial surgery	Skin flora: primarily staphylococci	Co-amoxiclav or cefuroxime
• Amputation	*S. aureus*, anaerobes if gangrenous	Co-amoxiclav or cefuroxime and metronidazole or vancomycin and metronidazole
Orthopaedic		
• Joint replacement surgery	Skin flora: primarily staphylococci	Co-amoxiclav or cefuroxime or flucloxacillin and gentamicin

If patient has previously had MRSA or is at high risk (e.g. nursing home resident), use teicoplanin or other gylcopeptide.
For β-lactam allergy, replace co-amoxiclav or cefuroxime with teicoplanin +/− ciprofloxacin.

Table 39.11 Suggested cephalosporin-free antimicrobial prophylaxis for surgical site infection (adapted from SIGN, 2008)

Type of surgery	Suggested antimicrobials	Alternatives for penicillin allergy
Cardiothoracic	Flucloxacillin +/– gentamicin	Teicoplanin or Co-trimoxazole
ENT, maxillofacial and oral	Amoxicillin + metronidazole or Co-amoxiclav	Clarithromycin +/– metronidazole or Clindamycin
Gynaecology	Gentamicin + metronidazole	
Lower GI	Gentamicin + metronidazole	
Obstetrics	Co-amoxiclav	Clarithromycin +/– metronidazole or Clindamycin
Orthopaedic	Flucloxacillin +/– gentamicin	Teicoplanin or Co-trimoxazole
Thoracic	Flucloxacillin or Co-amoxiclav	
Upper GI	Gentamicin	
Urology	Gentamicin	
Vascular	Flucloxacillin +/– gentamicin (+metronidazole for amputations)	Co-trimoxazole or Teicoplanin

GI = gastro-intestial

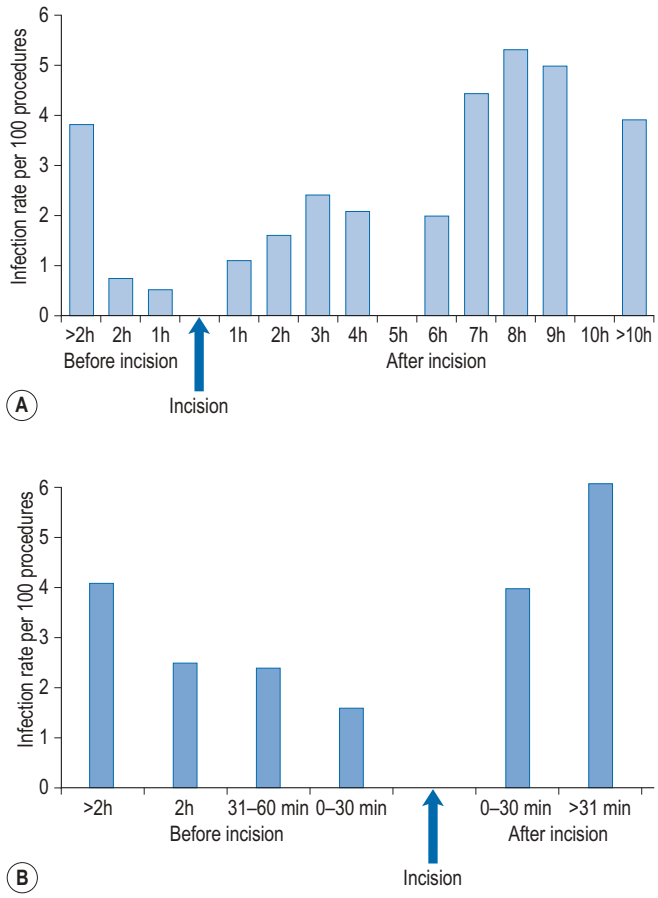


Fig. 39.5 Timing of antimicrobial prophylaxis administration and infection rate. Study A: The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection (Classen et al., 1992). Study B: Trial to reduce antimicrobial prophylaxis errors (Steinberg et al., 2009). Taken from Mandell et al. (2010). Reproduced with kind permission from Elsevier.

be delayed at short notice, sometimes between the time the patient leaves the ward and arrives at the theatre, it is sensible for the administration of antimicrobials to be transferred from ward staff to the operating team when prophylaxis can be given around the time of induction of anaesthesia.

The optimum time to administer prophylactic antimicrobials before incision is probably 30 min, but national recommendations vary from less than 30 min (SIGN, 2008) to 60 min (NICE, 2008a) prior to incision. Figure 39.5 represents the two major studies undertaken to identify the optimum time for administration of prophylaxis. Both studies determined that post-incision administration of antimicrobials significantly increased the risk of surgical site infection.

Historically, the only occasion where antimicrobial administration has been delayed to after the incision is Caesarian section, where antimicrobials are given after cross clamping the umbilical cord to prevent drug delivery to the neonate. However, it is recognised that this does not provide the mother with adequate tissue levels at the time of incision and two studies have shown that antimicrobials can be given safely before incision without adversely affecting the neonate (Sullivan et al., 2007; Thigpen et al., 2005).

When a tourniquet is used during orthopaedic procedures to minimise bleeding, the antimicrobial should be infused before inflating the tourniquet. This ensures adequate tissue levels are achieved at the site of surgery (Bratzler and Houck, 2004).

Certain practical issues should be considered when selecting an antimicrobial, for example, the requirement for intravenous infusion or safe intravenous bolus administration. An antimicrobial, which requires to be administered over a long period, for example, vancomycin 1 g over nearly 2 h, is much less likely to be given completely compared to teicoplanin, which is administered as a bolus.

To improve the timing of antimicrobial prophylaxis administration, the World Health Organisation (WHO) have introduced a question in their surgical safety checklist. The question *'Has antimicrobial prophylaxis been given within the last 60 minutes?'* is to be asked aloud before incision.

Repeat doses

Although single dose prophylaxis regimens are widely advocated (DH/HPA, 2008; NICE, 2008a; SIGN, 2008), many surgeons continue to use prolonged courses of 'prophylaxis' often for several days, without a clear evidence base. For some procedures, the optimum duration of prophylaxis is not known and 24–48 h prophylaxis is considered acceptable, for example, for open heart surgery (SIGN, 2008).

Where single dose prophylactic regimens have been adopted, the need for dosage adjustment in patients with reduced ability to excrete the drug (usually due to renal impairment) becomes unnecessary. This is because it is unlikely that single doses will have significant dose related adverse effects and idiosyncratic reactions are dose independent. Although the half-life of many drugs used is relatively short (1–2 h in normal volunteers), surgical patients often have slower clearance of antimicrobials from the blood. This concept will probably also hold true for prophylactic regimens lasting up to 48 h.

There are some situations in which it is necessary to prescribe additional doses of antibiotics to achieve the aim of adequate tissue levels at the time of wound closure. The additional doses may be needed when there is significant blood loss (>1500 mL) as plasma is effectively diluted by intra-operative transfusions and fluid replacement. Long operations may also need extra antimicrobial doses during the operation, but additional doses post-operatively do not provide an additional prophylactic benefit.

Antimicrobial administration by hospital theatre staff has practical implications for the route of administration. Ward-based administration of prophylaxis can be given orally if appropriate preparations exist, but this is impractical in sedated or unconscious patients. The oral route tends to suffer from variable absorption, especially in the presence of anaesthetic premedication, and this also makes it unsatisfactory. The intravenous route is the most reliable way of ensuring effective serum levels and is the only route supported by a substantial body of evidence.

A schematic model for the tissue concentration time profile of an antimicrobial agent used to prevent surgical site infection is presented in Fig. 39.6. After an initial dose of the antimicrobial agent, tissue concentrations reach their peak rapidly, with a subsequent decline over time. The goal of prophylaxis is for the antimicrobial tissue concentration to remain above the minimum inhibitory concentration (MIC) for the specific pathogens at the time of incision and throughout the procedure. The antimicrobial should be readministered during prolonged procedures to prevent a period where tissue concentrations are below the MIC (grey area). Failure to readminister antimicrobials appropriately may result in a period during which the wound is vulnerable. Recommendations for peri-operative re-dosing schedules are presented in Table 39.12. General guidance is to repeat doses of antimicrobials at intervals of 1–2 half-lives.

β-Lactam allergy

Penicillin and cephalosporin antibiotics have been the cornerstone of antimicrobial prophylaxis to prevent surgical site infections. Patients reported to be allergic to β-lactam antibiotics or other antimicrobials need to be carefully assessed, as alternatives may not be optimal. Alternatives are often glycopeptides, for example, teicoplanin or vancomycin, which are more expensive, often need to be given by infusion (vancomycin) and can increase selection for resistant bacteria. The prevalence of penicillin allergy in the general population is unknown. The incidence of self reported penicillin allergy ranges from 1% to 10%, with the frequency of life-threatening anaphylaxis estimated at 0.01–0.05% (or 1–5 in 10,000). More than 80% of patients with a self reported allergy to penicillin have no evidence of IgE antibodies on skin testing. Important details of an allergic reaction include signs, symptoms, severity, history of prior reaction, time course of allergic event, temporal proximity to administered drug, route of administration, other medication being taken and adverse events to other medication (Park and Li, 2005). Reactions to penicillins and other β-lactams occur because of allergy to the parent compound or the metabolites. The cross sensitivity between penicillins and cephalosporins is unknown, but has been variably reported to be up to 10%. Early cephalosporin preparations were contaminated with penicillins probably leading to an over estimate of cross sensitivity (Saxon et al., 1987). As the generation of the cephalosporin increases, the likelihood of cross sensitivity decreases (Pichichero and Casey, 2007). Those with a penicillin allergy showed an increased risk of allergic reaction to a first generation cephalosporin. First generation cephalosporins share a similar side chain to penicillin and amoxicillin. However, cross sensitivity to second and third generation cephalosporins was lower. The different side chains appear to play a more dominant role than the β-lactam ring in allergy.

Recent prospective studies have shown that the cross-reactivity to carbapenems and monobactams is very small. It is around 1% for imipenem and meropenem, and no cross-reaction has been reported for aztreonam (Frumin and Gallagher, 2009).

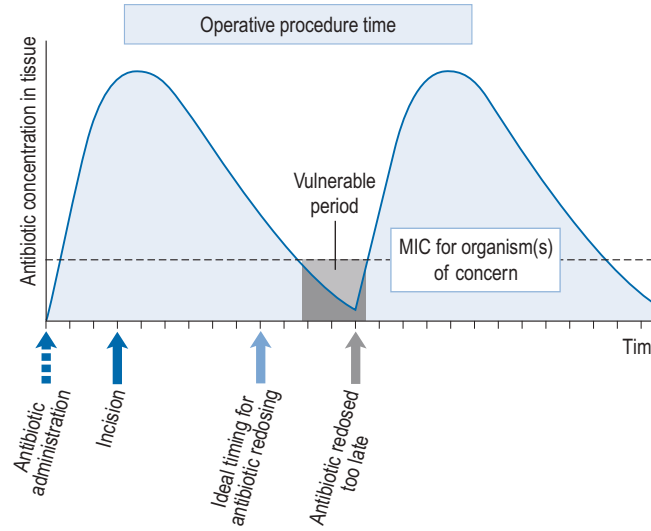


Fig. 39.6 Schematic presentation of tissue antibiotic concentration over time (Mandell et al., 2010). Reproduced with kind permission from Elsevier.

Table 39.12 Time for peri-operative re-dosing of antimicrobials (adapted from Bratzler and Houck, 2004; Gilbert et al., 2009)

Antimicrobials	Peak serum level (mg/L)	Half-life (h)	Time to redose
Cefuroxime 1.5 g IV	100	1.5	3 to 4 h
Ciprofloxacin 400 mg IV	4.6	4	4 to 8 h
Co-amoxiclav 1.2 g	Unknown	1.4 AM/1.1 CL	3 to 4 h
Co-trimoxazole 960 mg IV	9 TMP/105 SMX	7–12 TMP/8–15 SMX	8 to 12 h
Flucloxacillin 1 g IV	120–350	0.5	3 h
Gentamicin	N/A as many doses used	2.5	3 to 6 h unless >2 mg/kg; then do not redose
Metronidazole 500 mg IV	20–25	6–14	6 to 8 h
Vancomycin 1 g IV	20–50	4–6	6 to 12 h
Teicoplanin 200 mg IV	20	90–157	12 h

AM, amoxicillin; CL, clavulanic acid; TMP, trimethoprim; SMX, sulphamethoxazole.

The increased use of penicillins rather than first or second generation cephalosporins for surgical site infection prophylaxis is increasing the potential for adverse reactions. In addition, the current nomenclature for penicillin combinations, for example, co-amoxiclav, can often make it more difficult for staff to recognise penicillin containing antimicrobials. Current guidance on the use of β-lactams in patients with penicillin allergy is detailed in Table 39.13.

Topical or local antimicrobial prophylaxis

Many surgical procedures involving the use of implants or prostheses now use topical antimicrobials to prevent late surgical site infection. Examples include antimicrobial loaded cement for fixing hip and knee joint replacements into bone. Gentamicin is the only antimicrobial in commercially available products in the UK. Surgeons do add other antimicrobial agents, especially if replacing an infected prosthesis with choice based on culture and sensitivities.

In vascular surgery, synthetic grafts bonded with or soaked in rifampicin are frequently used, despite evidence showing that there was no decrease in infection rates at 1 month and 2 years (Stewart et al., 2006). There is some evidence to support the local delivery of gentamicin into wounds via collagen fleece impregnated with gentamicin and further research into this was recommended (NICE, 2008a); however, two recent randomised controlled trials have shown it not to be efficacious (Bennett-Guerrero et al., 2010a,b) The use of topical cefotaxime in contaminated surgery has been shown not to decrease peritonitis, and should not be used.

Table 39.13 Guidance on the use of β-lactam antibiotics in patients with penicillin allergy recommended by BNF (Joint Formulary Committee, 2010)

Allergic reaction	Action
Immediate hypersensitivity reaction to a penicillin	Avoid penicillins and cephalosporins
Minor rash – localised or widespread but delayed (>72 h)	Avoid penicillins, but cephalosporins are safe to use

Case Studies

Case 39.1

A patient is due to have an elective total hip replacement. As part of the routine, pre-admission screening is done, during which swab samples are taken. The patient is identified as being MRSA positive. The patient receives a five-day course of nasal mupirocin and topical chlorhexidine washes as 'decolonisation therapy' prior to the admission. The unit normally uses single dose co-amoxiclav as prophylaxis.

Question

Should there be a change to the routine antimicrobial prophylaxis for this patient?

Answer

A change to the routine antimicrobial prophylaxis should be recommended because co-amoxiclav is not active against MRSA. The commonly used terms 'decolonisation therapy' and 'MRSA eradication' falsely give the impression that this regimen eradicates MRSA carriage. In reality, it should be called 'suppression therapy' because these agents reduce the numbers of bacteria present

but often fail to eradicate MRSA carriage. *S. aureus* is still the predominant cause of surgical site infection and this patient remains at risk of an MRSA surgical site infection. As a consequence an agent that is active against MRSA should be used. Glycopeptides are the recommended antimicrobial class in this situation and there are two options: teicoplanin and vancomycin. Vancomycin needs to be given as an infusion at a maximum rate of 10 mg/min, which means that administering a 1-g dose will take nearly 2 h and may be impractical before skin incision. Teicoplanin can be given as a bolus, so is the best choice. Teicoplanin 400 mg intravenously can therefore be used instead of vancomycin 1 g intravenous. Where bone cement is required to secure the prosthesis, a commercially prepared bone cement containing gentamicin should also be used. Ideally, all antimicrobial prophylaxis guidelines or protocols should contain an option for MRSA positive patients. Administration of appropriate regimens is facilitated by MRSA screening of all elective patients.

Case 39.2

A patient with a severe allergy to penicillin is admitted for a hemicolectomy for cancer of the colon. The unit uses a single dose co-amoxiclav regime as antimicrobial prophylaxis for large bowel surgery.

Question

The junior hospital doctor asks your advice as to the antimicrobials to use instead of co-amoxiclav? What advice would you give?

Answer

Colorectal surgery still carries one of the highest surgical site infection rates of up to 10% for elective procedures. The usual bacteria found in these surgical site infections are *S. aureus*, gram-negative bacilli (e.g. *E. coli*) and anaerobes. Options for treatment include gentamicin and metronidazole, or ciprofloxacin and metronidazole. Centres that have a problem with *Clostridium difficile* infection may prefer to use gentamicin and metronidazole. There is evidence for the use of single dose regimes.

Case 39.3

A 73-year-old lady is seen in pre-admission clinic for assessment prior to a knee replacement. She has recently had *Clostridium difficile* infection in the community after being treated with a 1-week course of co-amoxiclav. She is asymptomatic now. The surgical team is reluctant to use its usual antimicrobial prophylaxis regime of co-amoxiclav, or cefuroxime or ciprofloxacin.

Question

The anaesthetist assessing the patient in pre-assessment clinic asks your advice on what to prescribe. The lady is currently being screened for MRSA. What advice would you give?

Answer

The most common pathogens in knee replacement surgical site infections are *S. aureus* and coagulase-negative staphylococci, although infection rates are low (0.2%, e.g. in Scotland). Depending on the result of the MRSA screening test, there will be different answers. If the lady is colonised with MRSA, she could receive a single dose of teicoplanin. Options for prophylaxis include flucloxacillin with gentamicin or teicoplanin, although the latter does not cover gram-negative bacteria. The use of gentamicin-containing cement would be recommended.

Case 39.4

A 72-year-old man is due for elective transurethral resection of the prostate (TURP) and is currently well with no signs of a urinary tract infection. Routine prophylaxis for surgical site infections on the unit is co-amoxiclav. The patient is known to have had a mitral valve replacement 2 years ago.

Question

You are asked whether the antimicrobial prophylaxis should be amended to cover this? What advice would you give?

Answer

NICE guidelines no longer recommend prophylaxis for patients at risk of endocarditis undergoing investigations involving the oral, gastro-intestinal or urogenital tract, in the absence of local infection (NICE, 2008b). The usual prophylaxis for this regimen should be recommended. If the patient had a urinary tract infection, this should ideally be treated before surgery.

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40 Tuberculosis

L. K. Nehaul

Key points

- In 2008, there were an estimated 9 million cases of tuberculosis (TB) and 2 million deaths from the disease worldwide.
- One-third of the world's population is infected with the tubercle bacillus.
- Adequate and effective treatment is essential to treat the individual, control the spread of TB and minimise the occurrence of drug-resistant disease.
- TB is caused by infection with *Mycobacterium tuberculosis*, *M. bovis* and *M. africanum*. *M. tuberculosis* accounts for around 99% of isolates in the UK.
- TB infection usually occurs by the respiratory route.
- People with HIV infection have an increased risk of developing active TB disease if co-infected with tubercle bacilli.
- Certain medical risk factors increase the risk of TB.
- Most treatment regimens in the developed world are of 6 months' duration and contain isoniazid, rifampicin and pyrazinamide, with ethambutol or streptomycin.
- Rifampicin, isoniazid and pyrazinamide are all potentially hepatotoxic. Isoniazid may cause a dose-dependent peripheral neuropathy, while ocular toxicity is the most important side effect of ethambutol.
- Multidrug-resistant TB is a problem in many parts of the world; extensively drug-resistant TB was first reported in 2006.

Introduction

Tuberculosis (TB) is a bacterial infection, treatable by anti-TB drugs. It is a global problem, with the incidence varying across the world. In 1993, an increase in reported cases of TB in countries across all continents led the World Health Organization (WHO) to declare TB a global emergency. The burden of TB in many countries is compounded in those who have co-infection with the human immunodeficiency virus (HIV). Of additional concern has been the increase in multidrug-resistant tuberculosis (MDR-TB), with outbreaks in different parts of the world. In 2006, the emergence of extensively drug-resistant tuberculosis (XDR-TB) was first reported. The treatment of drug-resistant TB is complex, costlier and of a longer duration than drug-susceptible cases.

Adequate and effective treatment is essential, both clinically for patients and also to control TB, as the BCG vaccine does not prevent infection. Successful control depends on a close working collaboration between clinical, microbiological, pharmacy, infection control and public health teams in managing patients and their contacts, and a shared understanding with primary care teams as to the role of all health professionals involved in TB.

Clinical and public health practice for bringing TB under control in the UK is underpinned by guidance from National Institute for Health and Clinical Excellence (2006) and the Joint Committee on Vaccination and Immunisation (Department of Health, 2006).

Aetiology

TB is caused by tubercle bacilli, which belong to the genus *Mycobacterium*. These form a large group but only three relatives are obligate parasites that can cause TB disease. They are part of the *Mycobacterium tuberculosis* complex. The UK data for 2008 show that *M. tuberculosis* was isolated in 99% of confirmed cases, *M. bovis* in 0.4% and *M. africanum* in 0.5% that year (Health Protection Agency, 2009).

Mycobacterium species include:

- *M. tuberculosis* complex*: M. tuberculosis*, *M. bovis*, *M. africanum*
- *Mycobacteria other than tuberculosis:* Around 15 are recognised *as pathogenic to humans and some cause* pulmonary disease resembling TB. They have been found in soil, milk and water. They are also referred to as atypical mycobacteria.
- *Mycobacterium leprae:* The cause of leprosy.

Clinical aspects

Infection with tubercle bacilli occurs in the vast majority of cases by the respiratory route. The lung lesions caused by infection commonly heal, leaving no residual changes except occasional pulmonary or tracheobronchial lymph node calcification (Heymann, 2004). About 5% of those initially infected will develop active primary disease (Hawker et al., 2005). This can include pulmonary disease, through local progression in the lungs, or by lymphatic or haematogenous spread of bacilli, to pulmonary, meningeal or other extrapulmonary

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involvement, or lead to disseminated disease (miliary TB). In the other 95%, the primary lesion heals without intervention but in at least one-half of patients, the bacilli survive in a latent form, which may then reactivate later in life. Infants, adolescents and immunosuppressed people are more susceptible to the more serious forms of TB such as miliary or meningeal TB.

Pulmonary (respiratory) TB is more common in the UK than extrapulmonary (non-respiratory) TB. Sites of extrapulmonary disease include the pleura, lymph nodes, pericardium, kidneys, meninges, bones and joints, larynx, skin, intestines, peritoneum and eyes. In the UK, the lymph nodes are the most common site for extrapulmonary disease. In 2008, 55% of cases were pulmonary and 21% involved the extrathoracic lymph nodes.

Pulmonary TB may arise from exogenous reinfection or endogenous reactivation of a latent focus remaining from the initial infection. If untreated, about 65% of patients will die within 5 years, the majority of these within 2 years. Completion of chemotherapy using drugs to which the tubercle bacilli are sensitive almost always results in a cure, even with HIV infection.

Incubation period

The incubation period from infection to demonstrable primary lesion or significant tuberculin reaction ranges from 2 to 10 weeks. Latent infection may persist for a lifetime. HIV infection appears to shorten the interval for the development of clinically apparent TB.

Transmission

Transmission occurs through exposure to tubercle bacilli in air-borne droplet nuclei produced by people with pulmonary or respiratory tract TB during expiratory efforts such as coughing or sneezing. In general, only the respiratory forms of TB (tuberculosis of the larynx is highly contagious but rarely seen in the UK) are infectious. Most infections are acquired from adults with post-primary pulmonary TB. The greatest risk of infection is to close, prolonged contacts, mainly household contacts. Between 90% and 95% of cases of TB in children are non-infectious (Davies, 2003). TB cannot be acquired from individuals with latent TB infection (LTBI).

Patients should be considered infectious if they have sputum smear-positive pulmonary disease (i.e. they produce sputum containing sufficient tubercle bacilli to be seen on microscopic examination of a sputum smear) or laryngeal TB. Patients with smear-negative pulmonary disease (three sputum samples) are less infectious than those who are smear positive. The relative transmission rate from smear-negative compared with smear-positive patients has been estimated to be 0.22 (British Thoracic Society, 2000).

Risk groups

Certain groups are at increased risk of LTBI and possibly TB disease if exposed. These include:

- close contacts of patients with TB, especially those with sputum smear-positive pulmonary disease
- casual contacts (e.g. work colleagues) if they are immunosuppressed
- people from countries with a high incidence of TB (40/100,000 population or greater).

People with certain medical conditions are at increased risk of developing active TB if they have LTBI. These medical risk factors are set out in Box 40.1.

Box 40.1 Examples of factors that increase risk of developing active tuberculosis if infected

- HIV positive
- Injecting drug users
- Solid organ transplantation, jejunoileal bypass or gastrectomy
- Haematological malignancy, for example leukaemia and lymphomas
- Chronic renal failure or receiving haemodialysis
- Receiving anti-TNFα treatment
- Silicosis

Impact of HIV infection

People with HIV infection have an increased risk of developing TB if exposed to infection. The estimated annual risk of TB in those with HIV infection and TB co-infection is around 10% as opposed to a 10% lifetime chance in someone infected with TB, but not HIV.

Drug-resistant TB

MDR-TB is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs. MDR-TB results from either primary infection with resistant bacteria or may develop in the course of a patient's treatment.

XDR-TB is a form of TB caused by bacteria that are resistant to isoniazid and rifampicin, that is, MDR-TB, as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs including amikacin, kanamycin or capreomycin (WHO, 2010).

Epidemiology

Epidemiology is a measure of the occurrence of a disease in different populations. It helps to identify population groups at increased risk of TB. The key measures for TB are the number of new cases in a specified period of time, usually 1 year, and the incidence rates, that is, new cases per 100,000 of the population. Incidence rates are a good comparative measure of differences in the occurrence of TB between countries or different sub-groups in the population, as they take into account the size of those groups. TB surveillance, which involves monitoring its occurrence and epidemiology, is an essential component of TB control programmes, because it helps to evaluate their effectiveness in reducing disease rates.

Global

Globally, it is estimated that TB causes about 2 million deaths worldwide each year. One-third of the world's population is infected with the tubercle bacillus. It is becoming the leading cause of death among HIV-positive people. Over 4 million cases of TB disease are notified annually although the estimated number of new cases is put at 9 million. The majority of cases occur in poor countries in the southern hemisphere (WHO, 2009).

The numbers of cases estimated to have occurred in 2008, globally and by WHO region, is presented in Table 40.1. Most cases of TB are in South East Asia, although the highest rates are in Africa.

In 2008, it was estimated that 440,000 people had MDR-TB worldwide, and one-third of these died. The brunt of the MDR-TB epidemic is borne by Asia, with almost 50% of cases worldwide estimated to occur in China and India. However, in some areas of the world, up to one in four people have drug-resistant TB. For example, 28% of all people newly diagnosed with TB in one region of North-Western Russia had the multidrug-resistant form of the disease (WHO, 2010).

UK

In the UK, since the late 1980s, there have been changes in the epidemiology of TB. Following a decrease in notifications over several decades, from the late 1980s cases of TB started to increase again.

A total of 8655 cases were reported in 2008 (Health Protection Agency, 2009). The overall rate across all population groups was 14.1 per 100,000 population. Of all cases, 39% occurred in the London region, where the rate was 44.3 per 100,000 population. Nineteen primary care organisations in England had a rate of 40 per 100,000 or over, all of which were in major urban areas. Rates of TB in England outside London varied from 5.7 per 100,000 in South-West England to 18.7 per 100,000 in the West Midlands. Incidence rates per 100,000 population were 8.7 in Scotland, 5.8 in Wales and 3.3 in Northern Ireland. The majority of cases (72%) were in the population born outside the UK and in those aged 16–44 years (61%). The TB rate was higher in those born abroad than among those born in the UK (86 compared with 4.4 per 100,000). This reflected higher rates of TB in people from high-incidence countries, mainly South Asia. The risk of TB is highest in the 5 years after arrival in the UK. TB can also occur as a travel-related disease in UK residents from high-incidence countries, who return to visit their country of birth and are exposed to TB. The numbers of cases by region in England, Wales and Northern Ireland, in 2008, is shown in Table 40.2.

Diagnosis

Symptoms

The symptoms and signs of TB include:

- Cough for 3 weeks or more/productive cough
- Sputum usually mucopurulent or purulent
- Haemoptysis not always a feature
- Fever may be associated with night sweats
- Tiredness
- Weight loss variable
- Anorexia variable
- Malaise.

Awareness of the disease

Awareness of TB on the part of health care professionals and of people in high-risk communities is essential to its control. Early diagnosis, especially of pulmonary TB, followed by prompt commencement of treatment can reduce the period of infectivity to other people, especially susceptible contacts, who might be at risk of the more serious forms of TB disease. Such contacts can include children in nurseries or schools or immunosuppressed patients in a hospital setting. Health care

Table 40.1 Estimated epidemiological burden of tuberculosis incidence globally and by WHO region (*Source*: WHO, 2010)

WHO region	Numbers (000s), 2008 (lower and upper bounds)	Rates per 100,000 population, 2008 (lower and upper bounds)
Africa	2800 (2700–3000)	350 (330–370)
Americas	280 (260–300)	31 (29–33)
Eastern Mediterranean	650 (580–740)	110 (99–130)
Europe	430 (400–460)	48 (45–51)
South-East Asia	3200 (2800–3700)	180 (160–210)
Western Pacific	1900 (1700–2200)	110 (95–130)
Global	9400 (8900–9900)	140 (130–150)

Table 40.2 Tuberculosis case reports and rates by UK region/country 2008 (adapted from Health Protection Agency, 2009)

UK region/country	Number of cases	Rate per 100,000 population
London	3376	44.3
West Midlands	1012	18.7
North West	745	10.8
Yorkshire and the Humber	647	12.4
East Midlands	517	11.7
South East	719	8.6
East of England	478	8.3
South West	297	5.7
North East	179	7.0
England	7970	15.5
Scotland	452	8.7
Wales	174	5.8
Northern Ireland	59	3.3

professionals should be particularly alert to symptoms suggestive of TB in health care workers or people working in childcare or institutional settings, and initiate investigations at the earliest possible opportunity. Such action can lead to the diagnosis of TB before it becomes infectious, thereby protecting vulnerable contacts.

TB should be considered in the differential diagnoses of patients with a chronic cough for which there is no other likely cause, or in individuals with chest infections not responding to treatment.

Clinical diagnosis

The clinical diagnosis of TB disease is based on the symptoms and signs in the patient together with chest radiography, microscopy of sputum (for acid-fast bacilli) followed by culture and tuberculin skin testing. Blood-based immunological tests, introduced in the last few years, will play an increasingly important role in TB diagnosis. These tests can distinguish between TB infection and previous BCG vaccination.

Investigations

Investigations are essential to confirm clinically suspected TB and should be arranged even if the diagnosis is strongly suspected on clinical grounds. Microbiological tests are crucial, especially for pulmonary disease, as they facilitate both the clinical and public health management of TB and ensure the appropriate implementation of infection control procedures for cases managed in healthcare settings.

Microbiological

Microbiological investigations are undertaken to assess the infectious state of the patient, and distinguish between infection with mycobacteria causing TB and other mycobacteria. They also determine the drug-susceptibility patterns of the infecting organisms, to ensure that the drugs prescribed will be effective in treating the individual patient. Investigations comprise microscopy, culture, drug-susceptibility testing and strain typing.

Direct microscopy of sputum is the simplest and quickest method of detecting the infectious patient, by looking for acid-fast bacilli. A minimum of three sputum samples, one of which should be early morning, should be collected from patients with suspected respiratory TB.

Direct microscopy is not as useful in non-pulmonary disease, any specimens taken should be sent for culture.

If conventional culture methods are used, such as the Lowenstein–Jensen medium, growth may take up to 6 weeks. Modern liquid cultures can produce results more quickly. Polymerase chain reaction (PCR)-based tests can also detect *M. tuberculosis* complex in clinical specimens.

A rapid test is available for assessing rifampicin resistance in individuals thought to have drug-resistant TB. A positive result indicates the need to assess susceptibility to other first-line anti-TB drugs. Drug-susceptibility testing still needs to be done on isolates grown on culture media.

DNA fingerprinting, or strain typing, is useful in the public health management of TB. In 2010, a new method, mycobacterial interspersed repetitive unit/variable number of tandem repeats (MIRU/VNTR) 24-loci strain typing, became available in the UK. Strain typing will help in establishing links between cases not previously identified, disproving links between apparent clusters of cases, and also in detecting cross-contamination in laboratories.

Tuberculin testing

Tuberculin testing is used to detect LTBI. Only the Mantoux test is now used but it should be carried out by health care professionals trained and experienced in its use. The standard Mantoux test consists of an intradermal injection of 2 TU of Statens Serum Institute (SSI) tuberculin RT23 in 0.1 mL solution for injection. In this test, 0.1 mL of the appropriate solution is injected intradermally, usually on the forearm, so that a bleb of around 7 mm is produced. The results are read 48–72 h later, although a valid reading can be obtained up to 96 h later. The transverse diameter of the area of induration is measured with a ruler and the result recorded in millimetres.

The interpretation of the test will depend on the clinical circumstances, including a past history of TB or exposure to TB. A diameter of induration of less than 6 mm is negative, that is, there is no significant hypersensitivity to tuberculin protein.

In the absence of specific risk factors for TB, induration of between 6 and 15 mm diameter may be due to previous TB infection, or BCG vaccination or exposure to non-tuberculous mycobacteria. An induration of more than 15 mm is strongly suggestive of TB infection or disease.

Chest radiography

The chest radiograph is a non-specific diagnostic tool, as TB may present as virtually any abnormality on chest radiography. This is why microbiological evidence of confirmation should be sought. Pulmonary TB may appear as bronchopneumonia with confluent shadowing, without cavitation. Cavitation may be seen, the incidence can vary between 10% and 30%. Uncharacteristic radiological patterns may occur in the presence of HIV infection (Davies, 2003).

Diagnosis in people with HIV

TB can occur early in the course of HIV infection and may therefore be diagnosed before the patient is known to be HIV positive. The possibility of HIV infection in people with TB should therefore be considered, and testing for the virus is appropriate in those with risk factors for HIV.

Early in the course of HIV infection, before serious immunodeficiency occurs, TB is more likely to present with typical clinical features, and a positive tuberculin skin test, with cavitation and/or pleural disease on chest radiography. In the late stages of HIV infection, atypical presentations are more likely with unusual chest findings and extrapulmonary disease. The chest radiograph may be normal in up to 40% of cases.

Public health action

TB is a statutorily notifiable communicable disease in the UK. Cases should be notified on clinical suspicion by the attending doctor to the 'Proper Officer' for communicable disease control of the local authority where the patient resides. This is usually the local Consultant in Communicable Disease Control. In Scotland, notifications are made to the Health Board. Notification enables public health action to be initiated and involves investigation of prolonged, close contacts who might be at risk of infection, mainly those living in the same household as the patient, to assess them for LTBI or active TB disease. It may also enable the source of the infection to be found and treated.

Latent TB infection (LTBI) is not notifiable. Public health action is not taken for infections caused by 'mycobacteria other than TB'.

Treatment

In treating TB, a number of factors are important:

- Choice of drugs
- Length of treatment
- Co-morbidity especially HIV infection, liver and renal diseases
- Adherence to treatment by the patient.

It is important to tailor the management of the patient according to his or her situation, rather than just focus on the drug treatment of TB, as other factors in the patient's life may affect adherence.

Drug treatment

Treatment with anti-TB drugs has two main purposes:

- to cure people with TB, provided the bacilli are drug sensitive;
- to control TB, by either preventing the development of infectious forms or reducing the period of infectivity of people with infectious disease.

TB had started to decline in the UK before the advent of chemotherapy, probably due to improved nutrition and social conditions. With the advent of effective anti-TB chemotherapy, patients no longer needed treatment in a sanatorium. Results with regimens containing isoniazid together with *p*-aminosalicylate (PAS) or ethambutol, and sometimes streptomycin, gave excellent results. Treatment was required for 18–24 months if relapse was to be prevented. The availability of pyrazinamide and, more importantly, rifampicin made shorter courses of treatment a possibility. Most regimens in the developed world now contain isoniazid and rifampicin, which are the two most important drugs. These are prescribed together with pyrazinamide and possibly with another agent, such as ethambutol.

Bacterial characteristics

There are three populations of the *M. tuberculosis* (MTB) organism. The first population is that of the actively growing extracellular bacilli. Large numbers of bacilli can grow extracellularly in pulmonary cavities within liquefied caseous debris. This is the population in which drug resistance develops most rapidly. The second population consists of slow-growing or intermittently growing bacilli, which are inside macrophages. These are fewer in number, but the intracellular environment is acidic and many drugs are not active in these conditions. The third population is made up of slower-growing bacilli, which grow in solid caseous material. This environment is neutral in pH, but the penetration of drugs into this area can be compromised by a poor blood supply.

Rifampicin is the only drug that is bactericidal against all three populations. Isoniazid, streptomycin and the other aminoglycosides are bactericidal against extracellular bacilli. Isoniazid is also bactericidal against intracellular organisms. Pyrazinamide is bactericidal only against intracellular organisms and works well in an acidic pH. All other first-line TB drugs are bacteriostatic. Of the alternative drugs, which can be used in the treatment of drug-resistant TB, the quinolones have the highest bactericidal activity against *M. tuberculosis*.

When considering a treatment regimen for TB, it must be remembered that viable bacilli for slow-growing or intermittently growing populations may persist if drugs are not continued for an adequate period of time. The patient's condition can then relapse after chemotherapy is completed.

Treatment

The recommended standard treatment regimen for respiratory and most other forms of TB in the UK is:

- rifampicin, isoniazid, pyrazinamide and ethambutol for the initial 2 months (initial phase)
- a further 4 months of rifampicin and isoniazid (continuation phase).

A longer period of treatment than the standard 6 months is needed for meningeal TB and where there is direct spinal cord involvement.

Patients should be started on the standard treatment regimen on clinical diagnosis and the doses of the first-line anti-tuberculous agents are shown in Table 40.3. The drugs used can be changed if drug-susceptibility testing shows evidence of resistance.

The purpose of the concurrent use of four drugs in the initial phase is to reduce the bacterial population as rapidly as possible and prevent the emergence of drug-resistant bacteria. In general, daily dosing schedules are recommended. Combination tablets can be used and have the advantage of preventing accidental or inadvertent single drug therapy, which can lead to acquired drug resistance within weeks in active TB. It is important, however, to ensure the combination product contains the required dose of the constituent drugs.

Patients with suspected drug reactions or drug-resistant TB should always be referred back to the specialist physician and the healthcare team supervising their treatment.

Respiratory TB

Respiratory TB is defined as active TB affecting any of the following:

- lungs
- pleural cavity
- mediastinal lymph nodes
- larynx.

The standard 6-month regimen, as set out earlier, is recommended for the treatment of active respiratory TB in:

- adults not known to be HIV positive
- adults who are HIV positive
- children.

Table 40.3 Dosages of first-line anti-tuberculous agents[a]

Drug	Forms available	Dosage				Reduce dose in	
		Adults daily	Adults intermittent (doses per week)	Children daily	Children intermittent (doses per week)	Renal failure	Liver failure
Rifampicin	Capsules 150 mg, 300 mg[b] Liquid 100 mg in 5 mL Injection for infusion 300 mg	450 mg/kg (<50 kg) 600 mg (>50 kg)	15 mg/kg (3)	10 mg/kg	15 mg/kg (3)	No	Only in severe liver failure
Isoniazid	Tablets 50 mg[b] Injection 25 mg/mL Elixir (special order)[c]	300 mg	15 mg/kg (3)	5–10 mg/kg	15 mg/kg (3)	Only in severe liver failure	In patients with acute or chronic liver disease
Ethambutol[f]	Tablets 100 mg, 400 mg[b] Mixture[c]	15 mg/kg[d]		As adult dose	30 mg/kg (3)	Yes	No
Pyrazinamide	Tablets 500 mg	1.5 g (<50 kg) 2.0 g (≥50 kg)	2.0 g[d] (<50 kg) (3) 2.5 g[a] (≥50 kg)	35 mg/kg		Yes	No
Streptomycin	Injection 1 g	750 mg (<50 kg) 1 g (<50 kg)	750 mg–1 g[e]	15 mg/kg		Yes	No

[a]Some of the doses quoted are not licensed but have been recommended by the British Thoracic Society.
[b]Also available as combined oral preparations.
[c]Mixture may be prepared extemporaneously.
[d]Doses refer to patients under 50 kg. Reduce by 500 mg for patients weighing less than 50 kg.
[e]Drug levels should be monitored to prevent toxicity.
[f]Acute calculation is required to reduce the risk of toxicity.

TB of peripheral lymph nodes

Trials have shown that 6 months of treatment are just as effective as 9 months for fully susceptible bacilli. The standard 6-month treatment regimen is recommended.

Meningeal TB

Patients with active meningeal TB (tuberculous meningitis) should be treated with rifampicin and isoniazid for 12 months together with pyrazinamide, and normally ethambutol, for the first 2 months. Ethambutol (and streptomycin if used in preference) only reach cerebrospinal fluid through inflamed meninges.

Care must be exercised when ethambutol is used in unconscious patients as a decline in visual acuity, a known side effect of ethambutol, cannot be assessed.

Meningeal TB is a serious disease and treatment must be started promptly. The stage at which the disease is diagnosed, and treatment started, most affects prognosis. Therefore, it is often justified to start a therapeutic trial of anti-TB drugs in the absence of a definite diagnosis.

The use of glucocorticoids is also recommended in the management of meningeal TB and is commenced at the same time as anti-tuberculous drugs. Consideration should be given to their gradual withdrawal within 2–3 weeks of initiation. The recommended doses (National Institute for Health and Clinical Excellence, 2006) are:

- Adults: equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg
- Children: equivalent to prednisolone 1–2 mg/kg, maximum 40 mg.

The more recent British Infection Society (BIS) guidelines for the diagnosis and treatment of TB of the central nervous system (CNS) in adults and children (Thwaites et al., 2009) recommend all patients with meningeal TB should receive adjunctive corticosteroids (dexamethasone) regardless of disease severity at presentation.

Bone and joint TB

The spine is the most common site for bone TB. Bone and joint TB are treated effectively with standard agents such as isoniazid and rifampicin for 6 months, together with pyrazinamide and a fourth drug, usually ethambutol in the initial phase (for 2 months). This recommendation covers active spinal TB and active TB at other bone and joint sites. Occasionally, surgery may be needed to either relieve spinal cord compression or correct spinal deformities.

Disseminated TB

Generalised (disseminated or miliary) TB must be treated promptly as there is appreciable mortality from delayed diagnosis and treatment. The standard 6-month regimen containing both isoniazid and rifampicin, with pyrazinamide and ethambutol in the first 2 months, is used. If there is evidence of CNS involvement, treatment should be the same as for meningeal TB.

Pericardial TB

Although TB of the pericardium is rare in the UK, it is potentially important because of the possibility of cardiac tamponade and constrictive pericarditis, which are associated with a significant morbidity and mortality. The standard 6-month treatment regimen is recommended for patients with active pericardial disease. Glucocorticoids should also be prescribed at the following doses (National Institute for Health and Clinical Excellence, 2006):

- Adults: a glucocorticoid equivalent to prednisolone at 60 mg/day
- Children: a glucocorticoid equivalent to prednisolone 1 mg/kg/day (maximum 40 mg/day), with gradual withdrawal of the glucocorticoid, starting within 2–3 weeks of initiation.

Treatment of TB in special circumstances

TB in children

The doses of drugs used in children are shown in Table 40.3. Doses are generally estimated to facilitate prescription of easily administered volumes of liquid or tablets of appropriate strength. Ethambutol should not routinely be used in young children, who would be unable to report visual disturbances should they occur. However, it may be used if there is toxicity or resistance to other agents.

Pregnancy

As there is a risk of TB to the fetus, treatment should be commenced whenever it is moderately or highly probable that a pregnant woman has TB. Standard therapy should be given, although streptomycin should not be used as it may be ototoxic to the fetus. It is considered safe for mothers to breast feed while taking anti-tuberculous treatment. Pyridoxine (vitamin B_6) supplementation (10–25 mg/day) is recommended for breastfeeding women taking isoniazid. Patients should be warned of the reduced effectiveness of oral contraceptives in regimens containing rifampicin, and advised to use other, non-hormonal contraceptives.

Renal disease

Patients with renal disease may be given isoniazid, rifampicin and pyrazinamide in standard doses as these drugs are predominantly eliminated by non-renal routes. Ethambutol undergoes extensive renal elimination and therefore dose reduction is needed. Monitoring serum concentrations has been suggested, but this might not be readily available in many centres. Streptomycin must be used with considerable caution to prevent toxicity and is best avoided in renal failure. Rifampicin may be given in standard doses to patients on dialysis. However, doses of the other agents need to be modified, and a number of different regimens have been suggested.

Liver disease

Monitoring of liver enzymes is recommended in patients with liver failure or in alcoholics because rifampicin, isoniazid and pyrazinamide are all potentially hepatotoxic. However, increases in transaminases at the start of anti-tuberculous treatment occur frequently. These are usually transient and not a reason for stopping treatment unless frank jaundice or hepatitis develops, in which case all drugs should be stopped. It is usually possible to restart treatment when transaminases have returned to pre-treatment levels.

Immunocompromised patients

Patients who are immunocompromised, including those with HIV infection, should be treated with normal first-line agents unless multidrug-resistant TB is suspected. Theoretically, these patients have a greater risk of relapse and may need to be treated for longer than the normal 6 months.

TB and HIV co-infection

Guidelines for the treatment of TB/HIV co-infection (Pozniak et al., 2009) recommend that co-infected patients are managed by a multidisciplinary team which includes physicians with expertise in the treatment of both TB and HIV.

If patients on anti-tuberculous therapy are started on highly active antiretroviral therapy (HAART), then antiretrovirals should be chosen to avoid interactions with TB therapy. The treatment for TB should only be modified when drug interactions with antivirals do not allow the optimal TB treatment regimen. In some cases, a longer duration of treatment for the TB may be needed.

Chemo-preventive therapy for TB is not recommended in HIV-infected patients. However, as HIV-infected people with LTBI are more likely to progress to active TB disease than people without HIV, the detection and treatment of a latent infection is important.

HAART is effective at reducing the incidence of new TB in HIV-infected people. HIV-positive patients should therefore be offered HAART.

Drug-resistant TB

Drug-resistant TB is a considerable problem worldwide. In the UK, however, the proportion of TB isolates showing resistance is low (in 2008, 6% were resistant to isoniazid, 1.5% resistant to rifampicin, and 6.8% resistant to any first-line drug). Drug resistance is an important issue in the management of TB as it may compromise the effectiveness of treatment and prolong the period during which patients are infectious to others. Isoniazid is the most usual agent to which resistance is seen. Multi-drug resistance is important because the main bactericidal drugs, isoniazid and rifampicin, are ineffective. Treatment has to be individualised, requires a complex regimen involving the use of multiple reserve drugs and can cost at least £50,000 to £70,000 each to treat (Table 40.4). It is recommended that treatment of these individuals is only carried out by physicians with experience in drug-resistant TB; in hospitals, when inpatient treatment is necessary, with appropriate isolation facilities (negative pressure rooms); and in close conjunction with specialist centres.

Monitoring treatment

In pulmonary TB, sputum examination and culture are the most sensitive markers of treatment success. Patients taking regimens containing rifampicin and isoniazid should be non-infectious within 2 weeks. If a patient does not become culture negative, it may be due to either drug resistance or non-adherence, the latter being more likely. Good adherence is essential if treatment is to be successful and checking this can be difficult, especially when a patient is unwilling to cooperate.

Adverse reactions

The major adverse reactions of the first-line drugs are shown in Table 40.5. Rifampicin, isoniazid and pyrazinamide are all potentially hepatotoxic, and liver function should be checked before treatment commences with these drugs. Transient increases in transaminases and bilirubin commonly occur at the start of treatment although there is no need to continue to monitor liver function in patients where pre-treatment liver function was normal. However, liver function tests must be measured if fever, malaise, vomiting or jaundice develop and all drugs should be stopped. Liver function should be allowed to return to normal, at which time treatment can be recommenced one drug at a time. Clinical hepatitis is rare although patients may complain of vague symptoms such as abdominal pain and malaise which may indicate impending hepatitis.

Rifampicin is usually well tolerated, but gastro-intestinal upsets, fever and rash can occur. It interacts with many medications, including methadone, protease inhibitors and non-nucleoside reverse transcriptase inhibitors used to treat HIV infection, macrolide antibiotics, warfarin and hormonal contraceptives. It will colour the urine orange-red within approximately 4 h of a dose.

Hypersensitivity reactions or rashes may occur with any of the drugs. However, the most important, although rare, is caused by rifampicin and can be quite severe. It is more prevalent during intermittent treatment and presents as a flu-like syndrome, sometimes with abdominal pain and respiratory symptoms. This usually resolves on reverting to a daily dosage. However, if more serious effects occur, such as renal impairment or haematological abnormalities, the drug should be stopped and never restarted.

Isoniazid can cause fever, skin rashes and a dose-dependent peripheral neuropathy, probably due to depletion of vitamin B_6. This reaction is rare at recommended doses, but certain patient groups which include problem drinkers ('alcoholics') and pregnant women are at greater risk and should receive pyridoxine supplementation at a dose of 10–25 mg/day.

Pyrazinamide can cause hepatitis. This is not increased when the drug is given with isoniazid and rifampicin in the standard 6-month treatment regimen. However, when hepatic

Table 40.4 Reserve drugs: dosages and side effects (British Thoracic Society Joint Tuberculosis Committee, 1998)

Drug (once daily)	Children	Adults	Main side effects
Streptomycin	15 mg/kg	15 mg/kg (max dose 1 g daily)	Tinnitus, ataxia, vertigo, renal impairment
Amikacin	15 mg/kg	15 mg/kg	As for streptomycin
Capreomycin		15 mg/kg	As for streptomycin
Kanamycin		15 mg/kg	As for streptomycin
Ethionamide or prothianamide	15–20 mg/kg	<50 kg, 375 mg twice a day ≥50 kg, 500 mg twice a day	Gastro-intestinal, hepatitis; avoid in pregnancy
Cycloserine		250–500 mg twice a day	Depression, fits
Ofloxacin		400 mg twice a day	Abdominal distress, headache, tremulousness
Ciprofloxacin		750 mg twice a day	As ofloxacin plus drug interactions
Azithromycin		500 mg	Gastro-intestinal upset
Clarithromycin		500 mg twice a day	As for azithromycin
Rifabutin		300–450 mg	As for rifampicin; uveitis can occur with drug interactions, for example macrolides. Often cross-resistance with rifampicin
Thiacetazone	4 mg/kg	150 mg	Gastro-intestinal, vertigo, conjunctivitis, rash. Avoid if HIV positive (Stevens–Johnson syndrome)
Clofazimine		300 mg	Headache, diarrhoea, red skin discolouration
PAS sodium	300 mg/kg	10 g every morning or 5 g twice a day	Gastro-intestinal, hepatitis, rash, fever

PAS, *p*-aminosalicylate.

Table 40.5 Major adverse reactions of first-line anti-tuberculous drugs

Drug	Common reaction	Uncommon reaction
Isoniazid		Hepatitis, cutaneous hypersensitivity, peripheral neuropathy
Rifampicin		Hepatitis, cutaneous reactions, gastro-intestinal reactions, thrombocytopaenic purpura, febrile reactions, 'flu syndrome'
Pyrazinamide	Anorexia, nausea, flushing	Hepatitis, vomiting, arthralgia, hyperuricaemia, cutaneous hypersensitivity
Ethambutol		Retrobulbar neuritis, arthralgia

toxicity occurs, liver enzymes are elevated for a longer time than with rifampicin or isoniazid. If patients have known pre-existing hepatic dysfunction, the use of pyrazinamide should be carefully considered.

Ethambutol ocular toxicity (optic neuritis) is by far the most important side effect of ethambutol. Some patients with pre-existing ocular problems, for example those with diabetes, may be at greater risk of toxicity. Daily doses of 30 mg/kg or more increase the likelihood of toxicity, as does the administration of standard daily doses (15–25 mg) to patients with impaired renal function.

Patients should be tested for both visual acuity and red-green colour discrimination before treatment. If toxicity develops, the drug must be stopped promptly. This should lead to a gradual improvement in vision. Permanent damage may occur if the drug is continued.

In children older than 5 years of age, a dose of ethambutol of 15 mg/kg has been shown to be safe (Trebucq, 1997). A baseline ophthalmological assessment is important in children as in adults and should be repeated after 1–2 months.

Chemoprophylaxis

The use of chemoprophylaxis is important in preventing vulnerable individuals with LTBI from developing active TB disease. Without chemoprophylaxis, 40–50% of infants and 15% of older children with LTBI will develop active TB disease in 1–2 years. Prophylaxis is usually with isoniazid alone for 6 months or rifampicin and isoniazid for 3 months. Detailed guidance as to when isoniazid or rifampicin and isoniazid should be used has been produced by National Institute for Health and Clinical Excellence (2006).

BCG vaccine

BCG vaccine contains a live, attenuated strain derived from *M. bovis*. It does not protect against infection, but it prevents the more serious forms of disease such as miliary TB and meningeal TB. The BCG immunisation programme in the UK is now a risk-based programme, the key part being a neonatal programme targeted at protecting those children most at risk of exposure to TB, particularly from the more serious forms of the disease (Department of Health, 2006). Most age groups require a Mantoux test prior to being offered BCG vaccine.

Patient care

It is possible to cure virtually all patients with TB infection or disease provided that an adequate regimen, to which the bacilli are susceptible, is prescribed and the patient complies with treatment. By far the largest cause of treatment failure is non-adherence by the patient. This has serious consequences: treatment may fail and disease may relapse, in some cases with resistant organisms. A patient with infectious TB who does not adhere to treatment is a public health hazard.

Factors affecting adherence

A number of studies have shown that adherence falls as the number of tablets to be taken per day increases, and falls still further if doses have to be taken frequently through the day. Ideally, the least number of tablets should be given. Patients may fail to adhere because they feel better and do not appreciate the need to continue with their medication. Lack of clarity of instructions, written, verbal or other, may compromise adherence, particularly if the patient is confused by conflicting advice from different health care professionals. Finally, adverse effects, or symptoms perceived to be adverse effects, may reduce adherence.

Improving patient adherence

Anti-TB therapy should be prescribed once a day using as few tablets as possible. Single daily dosing enables patients to fit their medication into their daily routine. Rifampicin and isoniazid are both well absorbed when taken on an empty stomach. However, absorption is reduced and delayed when taken with or after food. It is therefore recommended that both should be taken 1 h before food to rapidly achieve peak blood levels. It is usually recommended that patients take their medication before breakfast. Cueing tablet taking to a regular activity may improve adherence in some patients.

The number of tablets to be taken each day may be reduced by using combination preparations of which several are available. Some, for example Rifater®, contain ratios of rifampicin, isoniazid and pyrazinamide that differ slightly from the dosages recommended by the British Thoracic Society. Combination preparations may not be suitable for use in children as the required dose regimens differ from those of adults.

Formulation

With the exception of streptomycin, first-line agents are usually administered orally. There is a liquid preparation of rifampicin available for patients who cannot take tablets or capsules. In patients who are severely ill, and cannot take oral medication, rifampicin may be given intravenously, and isoniazid can be administered by both the intravenous and intramuscular routes.

Information for patients

Written instructions and/or patient information leaflets (PILs) may be offered to support verbal counselling if there is any doubt as to the patient's understanding. It should be emphasised that the disease will be cured, but this will take some months and the tablets will need to be taken as prescribed even if the patient feels better. Some patients will adhere initially while they are unwell but will fail to adhere later as they begin to feel better.

The occurrence of some adverse effects may require discontinuation of a drug, but others are harmless. The patient should be told which side effects to expect and which require referral to a member of the healthcare team. Again, written instructions may be helpful.

A number of patients from abroad have a poor command of English. TB Alert has produced leaflets on the treatment of TB for patients. These can be found at the TB Alert website (http://www.tbalert.org/), and are available in languages other than English.

On occasion, drugs which are not licensed for use in the UK although licensed abroad are prescribed for TB. These may be obtained on a named-patient basis through recognised specialist wholesalers. Patients who receive these medicines require specific counselling to help them understand the special circumstances surrounding their use and receive appropriate patient information.

Directly observed therapy (DOT)

DOT, where the patient is observed taking their antituberculous medication by a health care professional, is not needed for most cases of active TB. A risk assessment for treatment adherence should be undertaken in all patients, and

DOT regimens considered where non-adherence to treatment might be a problem, for example in street- or shelter-dwelling homeless people with active TB and patients with a history of non-adherence. This latter group includes individuals with chronic alcohol or other social problems.

DOT regimens may be fully or partially intermittent. In the latter, four drugs (isoniazid, rifampicin, pyrazinamide and either ethambutol or streptomycin) are given daily for 2 months followed by rifampicin and isoniazid two or three times weekly for the subsequent 4 months. For most drugs, the doses are increased when given intermittently and these are shown in Table 40.3. Trials of intermittent regimens have shown treatment is as effective when given intermittently as when given daily.

Counselling points

It is now a requirement for patients to be provided with a PIL for medication they are taking. Patients should be advised to read the PIL. The TB doctor, nurse and pharmacist should provide them with other relevant information orally. Patients taking rifampicin should be told that the drug will cause a harmless discolouration of their urine and other body fluids, for example sweat and tears. The staining of tears is important if the patient uses soft contact lenses as these may be permanently stained. Gas-permeable and hard lenses are unaffected. Women using the oral contraceptive pill should be advised to use other non-hormonal methods of contraception for the duration of rifampicin treatment and for 8 weeks afterwards as the effectiveness of hormonal contraceptives is reduced by rifampicin.

Although ocular side effects are rare when ethambutol is taken in normal dosages, patients should be warned of this potentially serious side effect. They should be advised to stop the drug and report to their doctor if they notice any changes in vision, such as a reduction in visual acuity or changes in colour vision. This is especially important because visual changes are usually reversible on discontinuation of the drug but may be permanent if the drug is not stopped.

Case studies

Case 40.1

A man in his 40s is referred to a chest physician with a cough productive of sputum and a fever. A chest x-ray indicates bilateral pneumonia with apical involvement. A sputum smear reveals the presence of acid, alcohol-fast bacilli. His physician considers that TB is the most likely clinical diagnosis. This is subsequently confirmed microbiologically. The patient does not comply with treatment and needs to be admitted to hospital, but refuses. There are indications he might be disruptive if admitted into hospital.

Questions

1. What form of TB does this patient have?
2. What can be done to compel his admission to hospital?
3. Which groups of healthcare staff should be involved in arrangements for his admission to hospital?

Answers

1. This man has sputum smear-positive pulmonary TB, the infectious form of the disease, and poses a risk of infection to others.
2. Legal measures should be considered to have the patient compulsorily admitted to hospital. These are set out in the Public Health (Control of Diseases) Act 1984 for England and Wales, and the Health Protection Regulations 2010. This will involve an application to the magistrates court for compulsory admission to hospital under a legally binding order, to be signed by the magistrates. The hospital will need to have agreed to his admission.
3. He will need to be admitted to a side room. Given that he may be disruptive, a multidisciplinary team meeting should be held to agree a care plan in preparation for his admission. This should be discussed with the patient, including the reasons why he will need to be kept in isolation. This should take place prior to an application for a court order if the patient refuses admission to hospital.

Case 40.2

A woman in her 40s is admitted to hospital with shortness of breath. She has lived in sub-Saharan Africa. She subsequently develops a non-productive cough. Bronchial washings are smear negative for acid-fast bacilli, but *M. tuberculosis* is isolated from the sample. Early sputum samples are smear negative, but later samples are smear positive.

Questions

1. What form of TB does this patient have?
2. Should she be in isolation?
3. What treatment should she receive for her TB?
4. Is she at low or high risk for drug-resistant TB?
5. What further microbiological investigations would be essential?

Answers

1. She has pulmonary TB, indicated by her symptoms and chest x-ray.
2. She should be in isolation in a single room. If a risk assessment suggests she may have MDR-TB, advice should be sought from the Infection Prevention and Control Team as to whether she should be transferred to a negative pressure room.
3. She should be commenced on standard quadruple therapy, comprising rifampicin and isoniazid, supplemented with pyrazinamide and ethambutol for the first 2 months.
4. A history of residence in sub-Saharan Africa suggests she could be at risk of drug-resistant TB, in particular multiple drug-resistant TB. The change in sputum smear status, despite being on standard quadruple therapy, would certainly suggest drug resistance.
5. A PCR test should be done on the isolate to determine whether her infecting strains of tubercle bacilli are resistant to rifampicin. Tests should also be done to assess susceptibility to other drugs.

Case 40.3

A woman in her mid-20s is diagnosed as having sputum smear-negative pulmonary TB. Although she initially takes her anti-TB drugs, she does not attend follow-up clinics and her condition deteriorates. Her primary care doctor collects a sputum sample from her and persuades her to attend the chest clinic. The sputum smear is now positive and it is found she has continued to work, despite being advised not to do so.

Questions

1. What type of treatment regimen should be offered to this patient?
2. Who should be involved in planning this treatment regimen, and what arrangements should be put in place to ensure this works?
3. Should the patient's work contacts be screened?

Answers

1. Patients like this should receive supervised treatment (DOTS) three times a week in a convenient setting, such as at home.
2. There needs to be close collaboration between the physician responsible for treatment, the patient's primary care physician, TB nurse, pharmacist, the public health team and the health care professionals (often district nurses or health visitors in the UK) who will supervise treatment. The patient needs to be involved in discussions about these arrangements, as treatment will not be successful without her cooperation.
   The physician will need to adjust the treatment dosage in line with the thrice-weekly regimen, inform the general practitioner and ensure the correct prescriptions are issued. Those supervising treatment need a clear explanation of what is expected of them, including details of the drugs and dose, and duration of treatment. They also need to know what to do if the patient does not adhere.
3. The question of whether work contacts should be screened must be dealt with on an individual case basis. This usually involves the health protection (public health) team informing the patient of the need to inquire into work contacts, and getting the patient's agreement to approach a supervisor or manager in the workplace. A telephone conversation will provide initial information on the working environment and should be followed up by a visit if initial inquiries indicate a possible need to screen workplace contacts.

Case 40.4

A 40-year-old man with young children aged under 5 is diagnosed with infectious pulmonary TB, but is not taking his anti-tuberculous drugs. He has mental health problems for which he is on treatment and is a drug misuser. Arrangements are made for him to have home-based directly observed treatment (DOT) for TB, but these break down.

Questions

1. What other arrangements should be considered for his treatment?
2. What other options could be pursued if alternative arrangements cannot be put in place?
3. Might a community pharmacist have a role in assisting with the treatment of such a patient?

Answers

1. The mental health team responsible for his care could be asked if they would observe him taking treatment. However, they may be concerned about the possible risk to themselves from exposure to someone with infectious TB. The same difficulties could arise if admission to a secure mental health facility is considered. If the patient is not in contact with the drug service, their involvement is only possible if the patient agrees to engage with them.
2. If none of the options in (1) are possible in practice, the patient remains an infectious risk, especially to his children. The advice of child protection professionals should therefore be sought, and if necessary a referral made to social services. The children will not necessarily be taken into care, alternative ways of supporting child care will be sought but their safety is paramount.
3. Community pharmacists could have a role to play in supervising treatment and this should be discussed with them where appropriate. If they agree, arrangements can be put in place, including a discussion between the pharmacist and the patient as to the 'rules of engagement', that is what the patient can expect from the pharmacist and what the pharmacist expects from the patient.

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Useful websites

Immunisation against infectious disease 'The Green Book'
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917.

The truth about TB
http://www.thetruthabouttb.org/.

HIV infection 41

H. Leake Date and M. Fisher

Key points

- Untreated infection with the human immunodeficiency virus (HIV) leads to a progressive deterioration in the cellular immune response. After initial seroconversion, the infected individual may appear asymptomatic for a number of years, before developing symptomatic disease and/or acquired immune deficiency syndrome (AIDS).
- Complications arising from HIV infection can manifest in a variety of ways, usually as opportunistic infections or malignancies that are uncommon in the immunocompetent population.
- The aim of the treatment of HIV infection is to reconstitute, or prevent further deterioration of the immune system, with the intention of improving the quality and quantity of life. Management of HIV-related complications primarily involves the treatment and prophylaxis of opportunistic diseases.
- Currently available antiretroviral (ARV) agents are classified by their mechanism of actions as nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors and entry inhibitors.
- Antiretroviral agents are given in combination, usually of at least three agents, to improve efficacy and reduce the development of viral resistance.
- Treatment regimens are frequently complex and many of the drugs have significant toxicities and interactions with other drugs and with food. A high level of adherence to therapy is vital to ensure efficacy and prevent the emergence of resistant virus.

Epidemiology

In June 1981, five cases of *Pneumocystis jiroveci* (formerly known as *carinii*) pneumonia (PCP) were described in homosexual men in the USA. Reports of other unusual conditions, such as Kaposi's sarcoma (KS), followed shortly. In each of these patients, there was found to be a marked impairment of cellular immune response, and so the term acquired immune deficiency syndrome, or AIDS, was coined. In 1984, a new human retrovirus, subsequently named human immunodeficiency virus (HIV), was isolated and identified as the cause of AIDS.

Although initially described in homosexual men, it soon became apparent that other population groups were affected, including intravenous drug users and haemophiliacs. During the first decade, the epidemic grew and the importance of transmission via heterosexual intercourse and from mother to child (vertical transmission) was increasingly recognised.

In the UK, since 1999 the number of new HIV diagnoses has been higher in heterosexuals than in men who have sex with men (MSM), although more recently this trend has been reversing, due to a decline in diagnoses among people infected heterosexually abroad (particularly from Sub-Saharan Africa). The majority of heterosexuals with HIV have acquired their infection in countries of high prevalence, whilst the majority of ongoing transmission within the UK is still amongst men who have sex with men. Additionally, there is an increasing proportion of individuals with HIV who are living into older age. It is postulated that the ageing process is accelerated in the context of HIV infection, with a resultant increase in co-morbidities, such as cardiovascular disease, osteoporosis and osteopaenia, cancer, cognitive impairment, and hepatic and renal dysfunction.

The impact of treatment advances on the incidence of AIDS-related illnesses and mortality has been dramatic. However, the absolute number of new AIDS diagnoses and HIV-related deaths in the UK has plateaued, largely due to late presentation and the failure to diagnose HIV infection amongst the asymptomatic population.

Although the number living with HIV globally continues to rise, there are encouraging trends (including in many low- and middle-income countries) of declining prevalence and a slower rate of increase in new infections. Significant progress has been made since 2000 in increasing access to antiretroviral therapies in resource-poor settings. Although choice of agents and facilities for monitoring may be limited, and locally produced generic formulations are often used, the resultant impact on mortality has been as dramatic as that seen previously in resource-rich countries.

The virus has been isolated from a number of body fluids, including blood, semen, vaginal secretions, saliva, breast milk, tears, urine, peritoneal fluid and cerebrospinal fluid (CSF). However, not all of these are important in the spread of infection and the predominant routes of transmission remain: sexual intercourse (anal or vaginal); sharing of unsterilised needles or syringes; blood or blood products in areas where supplies are not screened or treated; and vertical transmission *in utero*, during labour or through breast feeding.

Pathogenesis

HIV, in common with other retroviruses, possesses the enzyme reverse transcriptase and consists of a lipid bilayer membrane surrounding the capsid (Fig. 41.1). Its surface glycoprotein molecule

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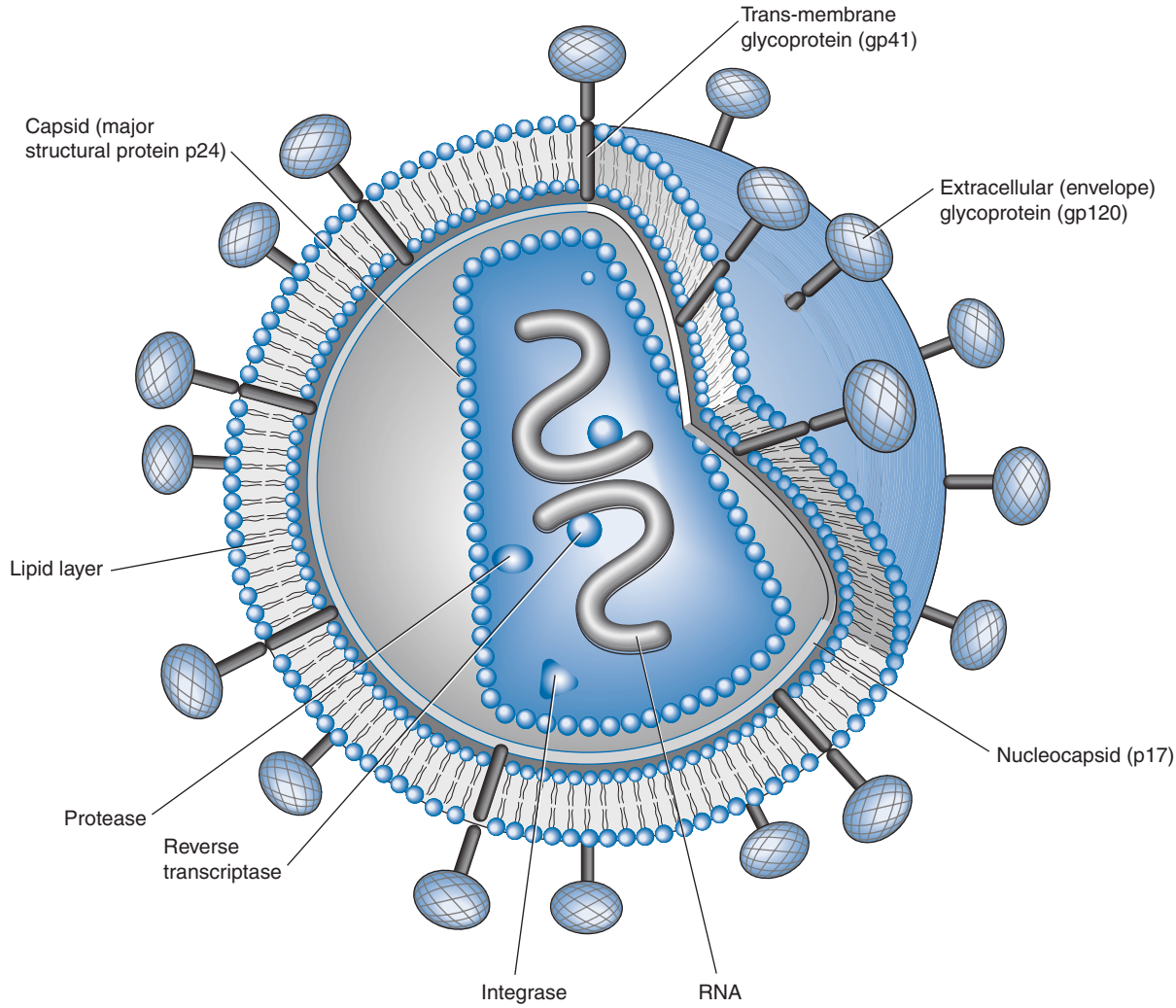


Fig. 41.1 Structure of the human immunodeficiency virus (HIV).

(gp120) has a strong affinity for the CD4 receptor protein found predominantly on the T-helper/inducer lymphocytes. Monocytes and macrophages may also possess CD4 receptors in low densities and can therefore also be infected. The process of HIV entry is more complex than originally thought, and in addition to CD4 attachment, subsequent binding to co-receptors such as CCR-5 or CXCR-4 and membrane fusion also occur (Fig. 41.2).

After penetrating the host cell, the virus sheds its outer coat and releases its genetic material. Using the reverse transcriptase enzyme, the viral RNA is converted to DNA using nucleosides. The viral DNA is then integrated into the host genome in the cell nucleus, where it undergoes transcription and translation, enabling the production of new viral proteins. New virus particles are then assembled and bud out of the host cell, finally maturing into infectious virions under the influence of the protease enzyme.

Immediately after primary HIV Infection (PHI, also known as 'seroconversion'), there is a very high rate of viral turnover. Equilibrium is then reached, at which stage the infection may appear to be clinically latent, but in fact, as many as 10,000 million new virions are produced each day.

Over time, as chronic infection ensues, cells possessing CD4 receptors, particularly the T-helper lymphocytes, are depleted from the body. The T-helper cell is often considered to be the conductor of the 'immune orchestra' and thus, as this cell is depleted, the individual becomes susceptible to a myriad of infections and tumours. The rate at which this immunosuppression progresses is variable and the precise interaction of factors affecting it is still not fully understood. It is well recognised that some individuals rapidly develop severe immunosuppression, whilst others may have been infected with HIV for many years whilst maintaining a relatively intact immune system. It is likely that a combination of viral, host (genetic) and environmental factors contributes to this variation.

Clinical manifestations

The sequelae of untreated HIV infection can be broadly considered in five categories:

- Opportunistic infections, that is, infections that would not normally cause disease in an immunocompetent host, for example, *P. jiroveci* pneumonia and cytomegalovirus (CMV)
- Infections that can occur in immunocompetent patients but tend to occur more frequently, more severely and

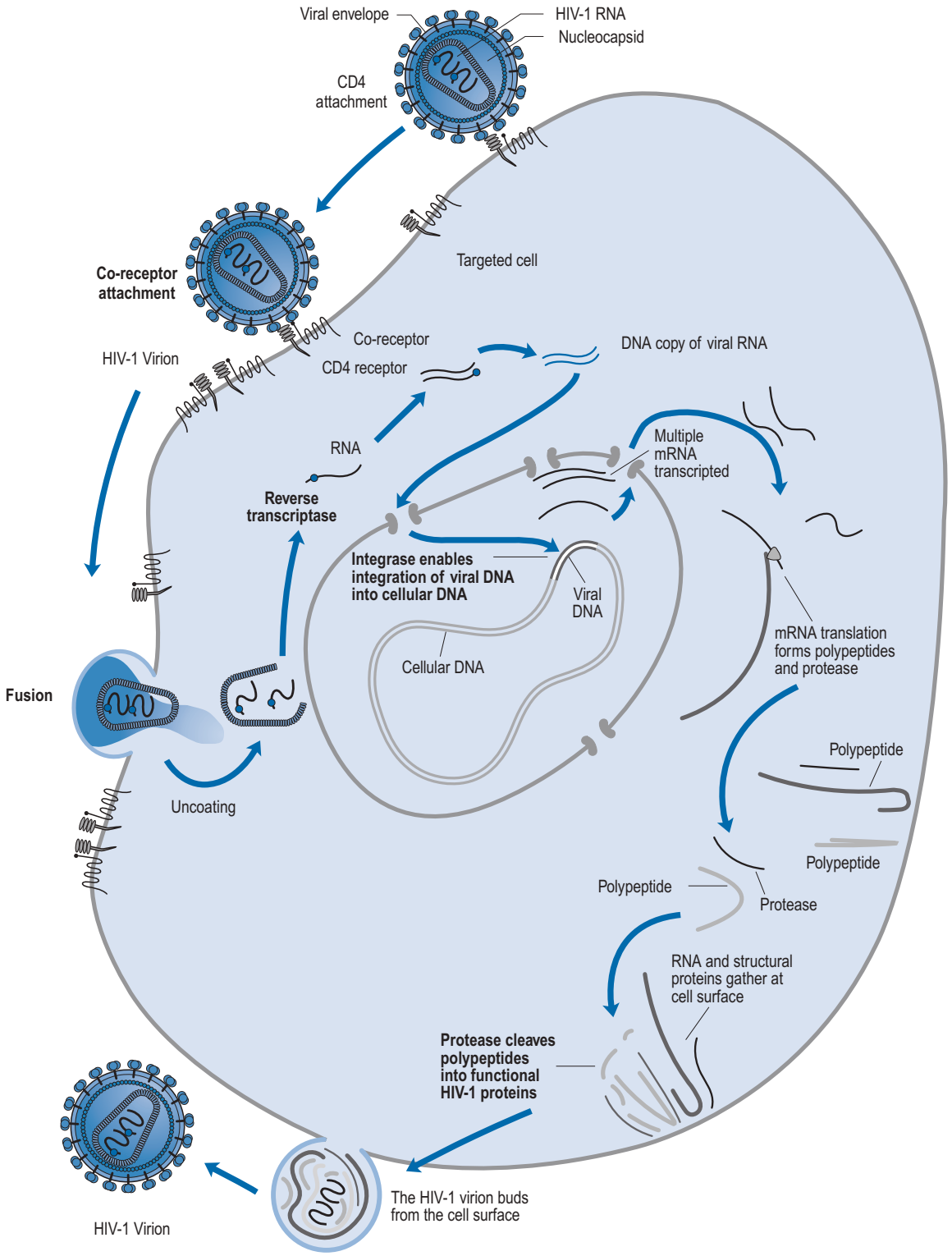


Fig. 41.2 Lifecycle of HIV and the sites of action of currently available antiretroviral agents (in bold).

often atypically in the context of underlying HIV infection, for example, *Salmonella*, herpes simplex and *Mycobacterium tuberculosis*

- Malignancies, particularly those that occur rarely in the immunocompetent population, for example, Kaposi's sarcoma and non-Hodgkin's lymphoma
- Direct manifestations of HIV infection *per se*, for example, HIV encephalopathy, HIV myelopathy and HIV enteropathy
- Consequences of chronic immune activation including premature cardiovascular disease, neurocognitive dysfunction, bone mineral density loss.

In addition, approximately 70% of individuals develop a flu-like illness at seroconversion. This primary HIV infection (PHI) is characterised by fever, arthralgia, pharyngitis, rash and lymphadenopathy. Rarely, the degree of associated CD4 count depletion may be sufficient to result in development of an opportunistic illness such as oropharyngeal/oesophageal candidiasis or *P. jiroveci* pneumonia.

Opportunistic infections generally fall into two categories:

- DNA viruses, for example, CMV and JC virus
- Intracellular pathogens, for example, *P. jiroveci*, *Toxoplasma gondii* and *Mycobacterium avium*.

Although the clinical course of HIV disease varies with each individual, there is a fairly consistent and predictable pattern that enables appropriate interventions and preventive measures to be adopted. Patients can be classified into one of three groups according to their clinical status: asymptomatic, symptomatic or AIDS. Symptomatic disease is characterised by non-specific symptomatology such as fevers, night sweats, lethargy and weight loss, or by complications including oral candidiasis, oral hairy leucoplakia, and recurrent herpes simplex or herpes zoster infections. AIDS is defined by the diagnosis of one or more specific conditions including *P. jiroveci* pneumonia, *M. tuberculosis* infection and CMV disease.

Investigations and monitoring

Current and previous infections

The initial diagnosis of HIV infection is made by the detection of antibodies against HIV. With improved technology, it is usually possible to detect antibodies within 3–4 weeks of infection, although individuals are advised that a 'window period' of up to 3 months after exposure is required before infection can be excluded. After confirmation of HIV infection, the patient is usually tested for prior exposure to a number of potential pathogens, including syphilis, hepatitis A, B and C, CMV, varicella zoster (VZV), and *T. gondii*. This can enable subsequent treatment (in the case of undiagnosed syphilis), vaccination (if no prior exposure to hepatitis A, B, or VZV), prevention (if no prior exposure to *Toxoplasma* and CMV), prophylaxis (if previous exposure to *Toxoplasma*) and can aid subsequent diagnosis (according to CMV or *Toxoplasma* status).

CD4 count

The level of immunosuppression is most easily estimated by monitoring a patient's CD4 count. This measures the number of CD4-positive T-lymphocytes in a sample of peripheral blood. The normal range can vary between 500 and 1500 cells/mm^3. As HIV disease progresses, the number of cells falls. Particular complications of HIV infection usually begin to occur at similar CD4 counts (Fig. 41.3) which can assist in

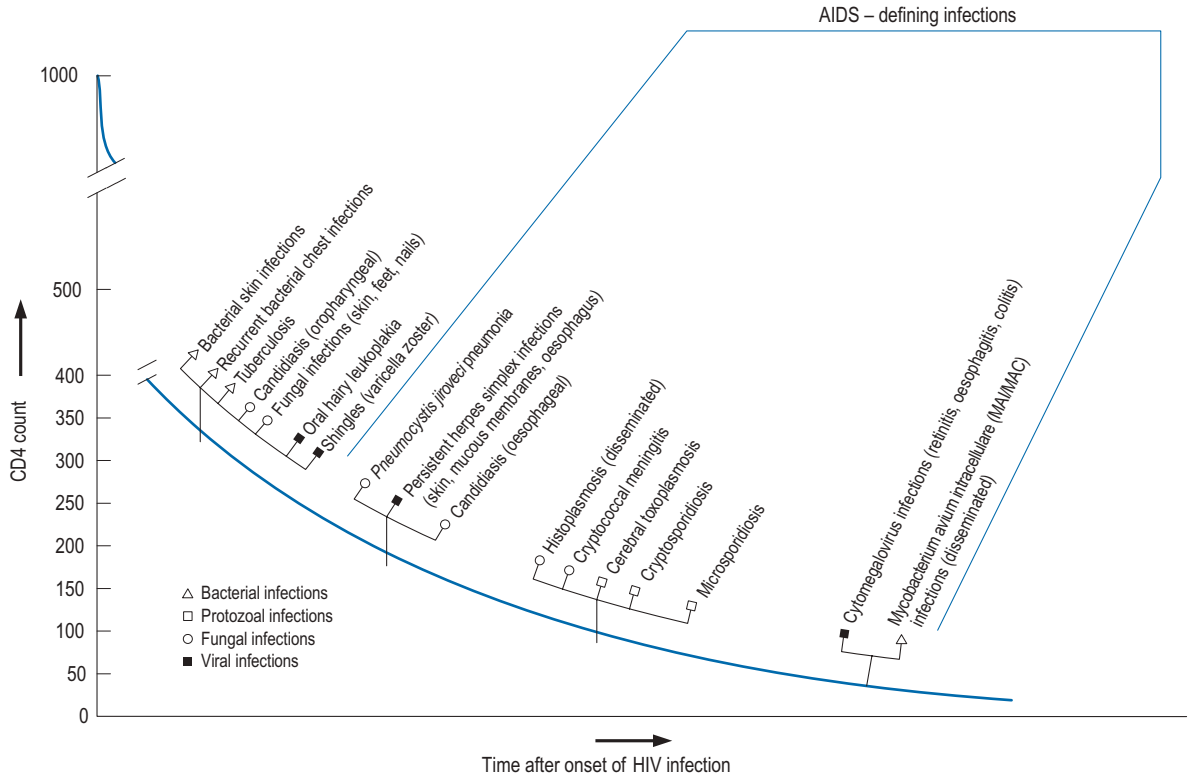


Fig. 41.3 Opportunistic complications of HIV infection and the CD4 count ranges at which they commonly occur.

differential diagnoses and enable the use of prophylactic therapies. For example, patients with a CD4 count of less than 200 cells/mm^3 should always be offered prophylaxis against *P. jiroveci* pneumonia. Similarly, both patient and clinician are likely to use the CD4 count as the major indicator of when to consider starting antiretroviral therapy.

Viral load

The measurement of plasma HIV RNA (viral load) estimates the amount of circulating virus in the blood. This has been proven to correlate with prognosis, with a high viral load predicting faster disease progression (Mellors et al., 1997). Conversely, a reduction in viral load after commencement of antiviral therapy is associated with clinical benefit. This measure, in combination with the CD4 count, allows patients and clinicians to make informed decisions regarding when to start and when to change antiviral therapies, enabling the more effective use of such agents. There are on-line calculators utilising viral load and CD4 count to model risk of disease progression or death based on large cohort studies.

Resistance testing

Due to the implications of transmitted (primary) resistance, it is recommended that all patients have a genotypic HIV resistance test performed soon after diagnosis; this will ensure that appropriate initial therapy is selected. Further resistance tests should be performed at any subsequent virological failure to direct therapy choice.

Tropism testing

Viruses may enter the cell using the CCR5 co-receptor, the CXCR4 co-receptor or both co-receptors. Those which just use one co-receptor are known as CCR5-tropic or CXCR4-tropic viruses; those which can use both receptor types are called dual-tropic. Where a mixture of virus populations is present, the term mixed-tropic is used. Different methods of determining tropism are currently under evaluation. The tests must be performed in real time as viral tropism changes as the disease progresses. If CCR5 inhibitors are to be used, it is essential to determine that the virus is CCR5-tropic, that is, that there is no significant use of the CXCR4 receptor.

Drug treatment

The drug treatment of HIV disease can be classified as antiretroviral therapy, the management of opportunistic infections or malignancies, the management of 'non-HIV-related' co-morbidities, and symptom control. For the first decade of the epidemic, most of the available drugs and therapeutic strategies were aimed at treating or preventing opportunistic complications and alleviating HIV-related symptoms. Whilst these are still important, there has been a shift in emphasis towards treatment aimed at reducing the HIV viral load, restoring immune function and reducing the potential consequences of co-morbidities.

Due to the speed at which new antiretroviral agents are being developed, comprehensive data on drug interactions, side effects, etc., are often lacking. Thus, the ability to apply general pharmacological and pharmacokinetic principles, together with common sense, is required.

The treatment of many of the opportunistic complications of HIV comprises an induction phase of high-dose therapy, followed by maintenance and/or secondary prophylaxis using lower doses. This is due to the high rate of relapse or progression after a first episode of diseases such as *P. jiroveci* pneumonia, cerebral toxoplasmosis (toxoplasmic encephalitis), systemic cryptococcosis and CMV retinitis. Where a cost-effective agent with an acceptable risk/benefit ratio exists, primary prophylaxis may be offered to individuals who are deemed to be at high risk of developing a particular opportunistic infection, for example, *P. jiroveci* pneumonia prophylaxis. Discontinuation of prophylaxis, both primary and secondary, is now usually possible in individuals who demonstrate immunological restoration on Highly Active Antiretroviral Therapy (HAART).

Paradoxically, this immunological restoration may result in apparent clinical deterioration with opportunistic infections during the first few weeks after initiation of HAART. This is known as immune reconstitution inflammatory syndrome (IRIS).

The goals of therapy in HIV-positive individuals are to:

- improve the quality and duration of life;
- prevent deterioration of immune function and/or restore immune status;
- treat and/or prevent opportunistic infections;
- relieve symptoms.

Antiretroviral therapy

Antiretroviral therapy is currently one of the fastest evolving areas of medicine. The specific details of treatment will therefore continue to change as new drugs emerge, although it is likely that the following general principles will remain:

- A combination of three antiretroviral agents, selected on the basis of treatment history and resistance tests, should usually be prescribed to increase efficacy and reduce the development of drug-resistant virus
- Wherever possible, a regimen should contain at least one drug that penetrates the central nervous system and confers protection against HIV-related encephalopathy/dementia
- Treatment strategies should be adopted that sequence drug combinations, being mindful of potential cross-resistance and future therapy options
- Given the crucial importance of a high level of adherence to these therapies, the regimen adopted for a particular individual should, wherever possible, be tailored to suit the daily lifestyle.

Many organisations, such as the British HIV Association (BHIVA), the European AIDS Clinical Society (EACS) and

the International AIDS Society (IAS), produce regularly updated guidelines on the use of antiretroviral therapy, for example, Gazzard et al. (2008). These guidelines include the most up-to-date considerations of:

- when to start therapy;
- what to start with;
- how to monitor, including use of therapeutic drug monitoring and resistance testing;
- when to switch therapy;
- what therapy to switch to;
- treating individuals who have been highly exposed to multiple agents;
- managing individuals with significant co-morbidities, for example, tuberculosis or hepatitis B/C.

Most studies evaluating triple combinations of antiretrovirals have been designed with so-called surrogate marker endpoints, measuring the effect on laboratory parameters such as CD4 count and HIV viral load. These trials are generally smaller and shorter in duration than clinical endpoint studies that are powered to measure the impact on survival and disease progression. The first large clinical endpoint trial that demonstrated the superiority of a triple combination over dual therapy was undertaken by Hammer et al. (1997). Following the results of this trial, the standard approach, where treatment is indicated, has been to use a combination of at least three agents. The reduction in morbidity and mortality associated with HAART has been confirmed in routine clinical practice, as well as in other trials (e.g. Palella et al., 1998; Smit et al., 2006). Subsequent clinical trials have largely been for licensing purposes and/or have served to refine therapeutic choices rather than to change the paradigm of treatment. The concept of intermittent rather than continuous therapy was evaluated in the SMART study but shown to be linked with an increased risk of co-morbidities not previously thought to be associated with HIV (such as cardiovascular disease, hepatic and renal failure) as well as HIV disease progression (El-Sadr et al., 2006). The use of protease inhibitor (PI) 'monotherapy' compared to conventional triple therapy has been evaluated in a number of small studies, for example, Arribas et al. (2009), and is being investigated in longer-term strategic studies. A large international study of early versus deferred treatment, to attempt to address the question of when to initiate treatment, is ongoing.

When to start therapy

Current UK guidelines recommend starting antiretrovirals when the CD4 count drops below 350 cells/mm^3. Therapy should be considered at a higher CD4 count in specific situations, for example, in the presence of an AIDS-defining illness or HIV-related morbidity.

Choosing and monitoring therapy

The majority of individuals are currently commenced on a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or two NRTIs and a boosted PI. The term 'boosted PI' refers to a combination of one PI combined with a low dose (usually 100–200 mg once or twice daily) of ritonavir, another PI. The ritonavir does not directly add to the antiretroviral activity of the regimen; it is used purely as a pharmacokinetic enhancer of the other PI, by increasing the maximum plasma concentration, C_{max}, due to inhibition of cytochrome P450 enzymes in the gut wall and/or extending the half-life, $t_{1/2}$, by inhibition of hepatic cytochrome P450 enzymes. Triple NRTI therapy is no longer recommended, as it is associated with unacceptable rates of virological failure. Alternative strategies, such as NRTI-sparing regimens and boosted PI monotherapy, are currently only routinely recommended in a research setting. More recently, integrase inhibitors have been approved for initial therapy and may be used as an alternative to NNRTIs or PIs.

The aim of initial therapy is to achieve viral load suppression in the plasma to levels below the detection limits of available assays (40 or 50 copies/mL). Such virological suppression is almost invariably accompanied by an elevation in CD4 count and clinical evidence of immune reconstitution. Whilst sustained suppression over many years is usually possible, viral rebound may occur and is often accompanied by the development of resistance to one or more agents in the combination. Upon confirmed virological failure, a resistance test is performed which will help to identify to which agents the virus may have adapted and the extent to which any such resistance mutations may confer cross-resistance to other available drugs. A second-line regimen is then constructed, wherever possible utilising a new class of drug to which the individual has not previously been exposed. Upon virological failure of subsequent regimens, the therapeutic options available become increasingly complex, but with the availability of more agents targeting different parts of the virus life cycle, virological suppression is still usually possible and should remain the goal of treatment.

Many of the antiretrovirals, particularly the PIs and NNRTIs, exhibit a wide range of interactions, especially with other drugs that are metabolised by the cytochrome P450 enzyme system, including prescribed, 'over-the-counter', herbal and recreational drugs. HAART failure (detectable viral load and drug resistance) has been documented following co-administration of hepatic enzyme inducers, including non-prescribed agents such as St John's Wort. Conversely, serious and even fatal toxicities due to enzyme inhibition by the PIs continue to be reported. These include Cushing's syndrome following concomitant use of fluticasone or budesonide inhaler or nasal spray with a PI. This highlights the necessity of taking a comprehensive drug history prior to starting or switching HAART and ensuring patients and prescribers are aware of the need to check the interaction potential of new medicines. General prescribing guidelines for antiretrovirals are presented in Box 41.1 whilst details of common side effects and interactions of the currently available agents are summarised in Tables 41.1 to 41.5.

The routine use of therapeutic drug monitoring is not recommended but blood levels of PIs and NNRTIs should be measured in selected patients, for example, during pregnancy, where there is liver impairment and where there are concerns regarding potentially interacting drugs (Gazzard et al., 2008).

Box 41.1 General prescribing and monitoring information for antiretroviral agents

- The Summary of Product Characteristics, current British National Formulary (BNF) and national guidelines should be consulted when managing the treatment of an HIV-positive patient.
- Adverse events should be reported. With greater exposure and long-term use, it is likely that more adverse events will be recognised. Some of these may be class effects associated with particular groups of antiretrovirals and should therefore be monitored even in new agents within a class. Examples include dyslipidaemia and diabetes mellitus with protease inhibitors, mitochondrial myopathy and lipoatrophy with NRTIs, rash with NNRTIs.
- There are limited data on the safety of many antiretroviral drugs when taken during pregnancy, or their long-term effects on babies/children. Updated safety information from the Antiretroviral Pregnancy Register is published twice yearly. Efavirenz has been shown to be teratogenic in animal studies, but comparable data are not available for the other antiretrovirals. Caution should therefore be exercised with all agents. Treatment of women who are planning conception or who are pregnant must be discussed with the relevant experts. All pregnant women who are treated with antiretrovirals should be reported prospectively to the Antiretroviral Pregnancy Register.

HIV mutates readily and resistance to some antiretrovirals, particularly reverse transcriptase inhibitors and integrase inhibitors, develops rapidly in the face of suboptimal treatment, for example, monotherapy or subtherapeutic blood levels. A high level of adherence to treatment is crucial to the sustained, successful outcome of antiretroviral regimens and has been the subject of much research. For example, in one study of people taking their first regimen containing nelfinavir, it was found that at least 95% adherence was required to achieve a sustained response in the majority (78%) of patients. The chances of treatment success declined as the level of adherence dropped, such that 80% of patients whose adherence was below 80% experienced virological failure. Virological success was also found to correlate with a better clinical outcome in terms of fewer hospitalisations, opportunistic infections and deaths (Paterson et al., 2000). Such clinical trial data have also been supported by clinical experience in the UK and elsewhere, although it has yet to be established if the level of adherence required is the same for all regimens and every patient. In view of this, patients should be advised to take HAART as close as possible to the same time every day and certainly within 1 hour of the agreed time each day. If they forget a dose, it should be taken as soon as they remember and then return to the original schedule.

There has been significant progress over recent years in reducing some of the physical burden of therapy, through the development of combination tablets and the use of strategies such as ritonavir boosting to reduce dietary restrictions and dosing frequency. Adherence aids such as pill boxes, medication record cards and alarms (e.g. on mobile phone) can also help to support adherence. However, practical issues are not the only barriers to adherence and the individual's health beliefs and motivation, particularly around HIV and antiretroviral therapy, should also be addressed before treatment is commenced, as these are likely to have a significant impact on outcome (Horne et al., 2004). Although there is little evidence to demonstrate what the optimal interventions to improve adherence are, multidisciplinary and multiagency approaches appear to be most useful (Poppa et al., 2003).

Treatment interruptions

For many reasons, including toxicity, cost and adherence, patients and clinicians have been interested in considering 'drug holidays' or treatment interruptions. However, this strategy is no longer recommended in routine practice (El-Sadr et al., 2006). It is now recognised that there are dangers associated with this approach because of CD4 decline, disease progression, mortality related to co-morbidities, for example, cardiovascular disease, and viral load rebound associated with increased transmission risk and a seroconversion-like syndrome. Further, as different anti-HIV medications have different half-lives, there may be a risk of functional monotherapy, particularly with NNRTIs, and the development of resistance if combinations are stopped abruptly in an unplanned fashion.

Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) involves the use of antiretroviral drugs to prevent infection with HIV after possible exposure, which may be recommended after occupational injuries (DH, 2008) or sexual exposure (Fisher et al., 2006). Whilst PEP is a largely unproven and unlicensed indication for the drugs used, it is supported by animal model data and case–control studies. Where recommended in guidelines, PEP is usually commenced as a 3–5-day starter regimen of two NRTIs and a boosted PI, followed by an ongoing course for a total of 4-week post-exposure. It is believed this will reduce the likelihood of infection by at least 80%, although toxicity issues are not insignificant. Therefore, the decision to prescribe or take PEP must reflect a careful risk/benefit evaluation. Studies of pre-exposure prophylaxis (PREP), using one or two antiretrovirals (orally or topically) before potential exposure to HIV, have so far yielded mixed results, but may offer additional options to reduce transmission.

Nucleoside and nucleotide analogue reverse transcriptase inhibitors

NRTIs are phosphorylated intracellularly and then inhibit the viral reverse transcriptase enzyme by acting as a false substrate. Nucleotide analogues only require two intracellular phosphorylations, whereas activation of nucleoside analogues is a three-stage process. The NRTIs licensed in the UK are:

Abacavir (Ziagen®)
Didanosine (ddI, Videx®)
Emtricitabine (FTC, Emtriva®)
Lamivudine (3TC, Epivir®)
Stavudine (d4T, Zerit®)
Tenofovir (Viread®)
Zidovudine (AZT, Retrovir®)

Table 41.1 General prescribing points for nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs)

Drug, names, manufacturer	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
Atripla® (efavirenz + emtricitabine + tenofovir) Bristol Myers Squibb/ Gilead	One tablet od	Tablet contains efavirenz 600 mg, emtricitabine 200 mg + tenofovir 300 mg	See entries for individual drugs	See entries for individual drugs
Abacavir (ABC) Ziagen® ViiV	300 mg bd 600 mg od 300 mg tablets 20 mg/mL oral solution	Can be taken with or without food	Usually well tolerated – Rash, headache, nausea and vomiting, diarrhoea, reduced appetite are most common side effects – Should only be prescribed if HLA B*5701 negative to reduce risk of *hypersensitivity* (5% incidence in unscreened populations): see BNF/SPC for full details. *Patient must NEVER be rechallenged if abacavir withdrawn due to suspected hypersensitivity*. Discuss with HIV team if reaction suspected. Counsel patient – Lactic acidosis (see BNF for more details) – May increase risk of cardiovascular disease	• Metabolism of methadone may be altered • Rifampicin, phenytoin, phenobarbitone may decrease abacavir levels – unclear significance in clinical practice • Concomitant treatment with abacavir and pegylated interferon + ribavirin associated with an increase in the risk of non-response to anti-HCV therapy – avoid ABC in someone receiving HCV treatment
Combivir® (CBV) (zidovudine + lamivudine) ViiV	One tablet bd	Tablet contains 300 mg zidovudine + 150 mg lamivudine	See entries for individual drugs	See entries for individual drugs
Didanosine (ddI) Videx® Bristol Myers Squibb	If >60 kg, 400 mg od (with tenofovir = 250 mg od) If <60 kg, 250 mg od (with tenofovir = 200 mg od) 400, 250, 200 and 125 mg e-c capsules 25 mg 'buffered' tablets (minimum two tablets/dose) Suspension (named patient)	– Must be taken on an empty stomach (although no food restrictions when taken with tenofovir) – Buffered tablets must be chewed, crushed or dispersed before taking – May be taken with clear apple juice to improve tolerability	– Nausea, bloating, diarrhoea (all may be reduced with e-c formulation) – Dry mouth – Pancreatitis (incidence<1%) (caution in patients with 'high' alcohol intake or history of pancreatitis) – Liver failure rare but reported. Monitor LFTs – Peripheral neuropathy (incidence <10%) – Hyperuricaemia – Lactic acidosis (see BNF for more details) – Shown to increase risk of cardiovascular disease	• Reduce dose in renal impairment (consult product literature) • Tenofovir, ribavirin, ganciclovir and valganciclovir may increase ddI levels ⇒ potential ↑ risk of toxicity • Caution when taking ddI *tablets* together with drugs adsorbed by antacids. No interaction with ddI *capsules* • Caution with drugs associated with pancreatitis
Emtricitabine (FTC) Emtriva® Gilead	200 mg od 200 mg capsules 10 mg/mL oral solution	Can be taken with or without food	– Headache most common – Also nausea, diarrhoea, dizziness; harmless skin discoloration – especially in darker skins – Lactic acidosis (see BNF for more details)	• No clinically significant interactions noted so far • Reduce dose in renal impairment (consult product literature) • Has anti-HBV activity
Kivexa® (abacavir + lamivudine) ViiV	One tablet od	Tablet contains 600 mg abacavir + 300 mg lamivudine	See entries under individual drugs (*NB*: Patients who have had a hypersensitivity reaction to ABC must NEVER be rechallenged with ABACAVIR, KIVEXA or TRIZIVIR)	• See entries under individual drugs

Lamivudine (3TC) Epivir® ViiV	150 mg bd 300 mg od 150 and 300 mg tablets Oral solution (10 mg/mL)	Can be taken with or without food	Generally well tolerated – GI disturbances, headache, anaemia and neutropenia have been reported but not common – Lactic acidosis (see BNF for more details); – Recurrent hepatitis can occur in chronic hepatitis B carriers on discontinuation of 3TC	• *Reduce dose in renal impairment (consult product literature)* • Increased risk of neutropenia with high-dose co-trimoxazole and ganciclovir, valganciclovir or foscarnet • Has anti-HBV activity
Stavudine (D4T) Zerit® *Bristol Myers Squibb*	If >60 kg, 40 mg bd If <60 kg, 30 mg bd 20, 30 and 40 mg capsules Oral solution (1 mg/mL)	Can be taken with or without food	– Peripheral neuropathy (following discontinuation symptoms may worsen before improvement noted) – Pancreatitis (rare) – *Lactic acidosis (see BNF for more details)* – Associated with increased risk of lipoatrophy/ lipodystrophy syndrome	• Caution with drugs associated with peripheral neuropathy (e.g. didanosine, vincristine, thalidomide, isoniazid)
Tenofovir (TDF) Viread® Gilead	300 mg od Tenofovir disoproxil 245 mg tablet (equivalent to Tenofovir disoproxil fumarate 300 mg)	Can be taken with or without food Can be dispersed in water	– Diarrhoea, nausea and vomiting, flatulence and headache most common (incidence>10%) – Renal impairment and hypophosphataemia reported – monitor serum creatinine and phosphate	• Reduce dose in renal impairment (consult product literature) • Mostly eliminated unchanged in the urine – possible interactions with nephrotoxic drugs or drugs that are excreted renally (e.g. ganciclovir, cidofovir, probenecid) – monitor closely • Has anti-HBV activity
Trizivir® (abacavir + lamivudine + zidovudine) ViiV	One tablet bd	Tablet contains abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg	See entries under individual drugs (*NB*: Patients who have had a hypersensitivity reaction to ABC must NEVER be rechallenged with ABACAVIR, KIVEXA or TRIZIVIR.)	• See entries under individual drugs
Truvada® (tenofovir + emtricitabine) Gilead	One tablet od	Tablet contains emtricitabine 200 mg + tenofovir 300 mg Can be dispersed in water	See entries under individual drugs	• See entries under individual drugs
Zidovudine (AZT) Retrovir® ViiV	Usual dose 250 mg bd (300 mg bd in Combivir and Trizivir) 100, 250 mg capsules 50 mg/5 ml syrup iv infusion	Can be taken with or without food (take with/after food to improve GI tolerance)	– Nausea, vomiting, headache, fatigue and muscle pain more common in first few – weeks and usually wear off – Haematological toxicities (e.g. neutropenia, anaemia) may develop after ~6 weeks – Myopathy may be associated with long-term therapy (>12 months) – Lactic acidosis (see BNF for more details) – Associated with increased risk of lipoatrophy/ lipodystrophy syndrome	• Clarithromycin can ↓ AZT absorption • Rifampicin may decrease AZT levels – unclear significance in clinical practice • Phenytoin levels may be altered • Increased risk of toxicity with ribavirin, probenecid and myelotoxic drugs (e.g. ganciclovir/valganciclovir and high-dose co-trimoxazole)

od, once daily; bd, twice daily; e-c, enteric coated; iv, intravenous; GI, gastro-intestinal; BNF, British National Formulary; LFTs, liver function tests; HCV, hepatitis C virus; HBV, hepatitis B virus.

Table 41.2 General prescribing points for non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Drug, names, manufacturer	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
Efavirenz (EFV) Sustiva® Bristol Myers Squibb	600 mg od (usually at night) – Increase to 800 mg od with rifampicin – Dose of oral solution: 720 mg od (24 ml) due to altered bio-availability 600 mg tablets 200 mg capsules 30 mg/mL oral solution	Can be taken with or without food. Manufacturer recommends taking on an empty stomach to improve tolerability Taken at night to minimise sedative effect, but can be taken during the day if preferred	– CNS disturbances (from sedation/feeling 'stoned'/dizzy and impaired concentration to vivid dreams, mood swings and hallucinations) – Caution in patients with previous or current psychiatric illness – Rash (in about 18% of adults) mostly in first 2 weeks, usually mild; severe rash rare – Raised LFTs – more common if hepatitis B or C co-infected – Hyperlipidaemia – monitor – Avoid in early pregnancy if possible – animal studies show teratogenic effects; effective contraception should be used	• Caution on stopping EFV-containing regimen due to long half-life • Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which affect these enzymes • Avoid clarithromycin, St John's Wort, ergotamines, caution with anticonvulsants • Mixed inhibitor and inducer of CYP450 enzymes – caution with other drugs metabolised by these enzymes; use alternatives wherever possible. Perform TDM on potentially affected drugs where indicated (e.g. phenytoin) • *Increases levels of midazolam* – avoid or start with low doses and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May get altered levels of methadone, erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®) and warfarin (monitor INR) among others
Nevirapine (NVP) Viramune® Boehringer-Ingelheim	200 mg od for first 14 days, then 200 mg bd. 400 mg od unlicensed dose. 200 mg tablets 50 mg/5 ml oral suspension	Can be taken with or without food. If dosing interrupted for >7 days, NVP must be restarted at lead-in dose (200 mg od for 2 weeks)	– Rash (in about 20%; most common in first 6 weeks); severe rash rare but monitor closely – Raised LFTs/hepatitis (check every 2 weeks for first 2 months) – Caution on restarting NVP if previously discontinued due to rash or hepatitis/↑LFTs – See BNF for more details – Also nausea, headache, sedation, fatigue – Should not be started in women with CD4 >250 cells/mm^3 or men with CD4 >400 cells/mm^3: greater risk of rash-associated hepatic events	• *Caution on stopping NVP-containing regimen due to long half-life* • Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes • *Avoid St John's Wort, rifampicin, caution with anticonvulsants* • Inducer of cytochrome P450 – caution with other drugs metabolised by these enzymes; use alternatives wherever possible. Perform TDM on potentially affected drugs where indicated • *May get altered levels of methadone and warfarin (monitor INR)* • May decrease levels of erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis) ®, vardenafil (Levitra®)
Etravirine (TMC-125) Intelence® Janssen	200 mg bd 400 mg od unlicensed dose 100 mg tablets	Take with food to improve bioavailability. Can be dispersed in water.	– Rash (in >10%) – severe rash (inc Steven-Johnson syndrome) reported but rare – Nausea – Diarrhoea, abdominal pain – Headache, pyrexia, fatigue	• *Caution on stopping etravirine-containing regimen due to long half-life* • Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes • *Avoid St John's wort, carbamazepine, clarithromycin, rifampicin* • Mixed inhibitor and inducer of cytochrome P450 enzymes – caution with other drugs metabolised by these enzymes; use alternatives wherever possible. Perform TDM on potentially affected drugs where indicated • *May get altered levels of methadone and warfarin (monitor INR)* • May get decreased levels of erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®)

od, once daily; bd, twice daily; BNF, British National Formulary; LFTs, liver function tests; TDM, therapeutic drug monitoring; INR, international normalised ratio.

Table 41.3 General prescribing points for protease inhibitors

Drug, names, manufacturer	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
Atazanavir (ATV) Reyataz® Bristol Myers Squibb	300 mg (with 100 mg ritonavir) od 400 mg (with 100 mg ritonavir) od with enzyme inducers or interacting meds 300, 200, 150mg capsules	Take with or after food to enhance bioavailability	Most common: – Nausea, diarrhoea, headache, rash, jaundice Also – Hyperbilirubinaemia (may need dose ↓ or stop if ≥ Grade 3 or 4) – Raised LFTs – more common in Hepatitis B or C co-infection – Does not appear to ↑ lipids – ECG changes – Other protease inhibitor 'class side effects', for example, lipodystrophy syndrome: body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort* • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids (avoid fluticasone and budesonide) • May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®) • *H_2 antagonists and proton pump inhibitors significantly decrease atazanavir levels* – discuss with specialist HIV team before co-prescribing. Avoid antacids within 2 h of ATV dose • Caution with erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®) – reduce initial dose (e.g. maximum dose sildenafil 25 mg in 48 h) • *If boosted, see ritonavir for full list of potential interactions*
Darunavir (TMC-114) Prezista® Janssen	600 mg bd (with ritonavir 100 mg bd) 800 mg od (with ritonavir 100 mg od) 400, 600 mg tablets	Take with food to improve bioavailability	Most common: – Nausea, vomiting diarrhoea, constipation, abdo pain – Headache, rash – Hyperlipidaemia Also – Raised LFTs. Caution in sulphonamide allergy – Other protease inhibitor 'class side effects', for example, lipodystrophy syndrome: metabolic/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort* • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with ergotamines, antiarrhythmics* • *Increases* levels of midazolam – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids (avoid fluticasone and budesonide) • May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®) • *Caution with statins (including pravastatin) – start with lowest dose and titrate according to response. Simvastatin CONTRAINDICATED* • Caution with erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®) – reduce initial dose (e.g. maximum dose sildenafil 25 mg in 48 h) • *See ritonavir for full list of potential interactions*

Continued

Table 41.3 General prescribing points for protease inhibitors—cont'd

Drug, names, manufacturer	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
Fosamprenavir (FAPV) Telzir® ViiV	700 mg bd (with 100 mg bd ritonavir) unlicensed doses: – 1400 mg od (with 200 mg od ritonavir) – 1400 mg bd (unboosted) 700 mg tablets 50 mg/mL oral solution	Can be taken with or without food	Most common: – Nausea and vomiting, diarrhoea – Rash – Fatigue Also – Raised LFTs – Hyperlipidaemia – Other protease inhibitor 'class side effects', for example, lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort, carbamazepine* • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders. (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®) • Caution with erectile dysfunction agents sildenafil (Viagra®), vardenafil (Levitra®) and tadalafil (Cialis®) – reduce initial dose (e.g. maximum dose sildenafil 25 mg in 48 h) • *If boosted, see ritonavir for full list of potential interactions.*
Indinavir (IDV) Crixivan® Merck Sharp and Dohme	800 mg every 8 h With ritonavir: 800 mg (with 100 mg ritonavir) bd or 400 mg (with 400 mg ritonavir) bd ↓ dose in hepatic insufficiency 200 and 400 mg capsules	Best on an empty stomach >1 h before food or >2 h after meals May take with light, low fat (<5 g fat) snacks. No food restrictions if with ritonavir. Store with desiccant. Drink >1.5 L water per day (even if taking with ritonavir)	– Nephrolithiasis – Hyperbilirubinaemia – Increases in AST and ALT – Rash, dry skin, pruritus, hair loss – Ingrown toenails – Taste perversion – Haemolytic anaemia – Other protease inhibitor 'class side effects', that is lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort, carbamazepine*. Indinavir increased by ketoconazole and itraconazole • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get – in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • *May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®)* • Administer indinavir and didanosine *tablets* at least 1 h apart (ok to take with e-c caps) • Caution with erectile dysfunction agents sildenafil (Viagra®), vardenafil (Levitra®) and tadalafil (Cialis®) – reduce initial dose (maximum dose sildenafil 25 mg in 48 h) • *If boosted, see ritonavir for full list of potential interactions*

Kaletra® (LPV/r) (lopinavir + ritonavir) Abbott	2 tablets bd 5 ml bd (=400/100 mg bd) 4 tablets/10 ml od (not recommended if >3 protease inhibitor resistance mutations present) Tablets: 200 mg lopinavir with 50 mg ritonavir; 100 mg lopinavir with 25 mg ritonavir 400/100 mg lopinavir/ritonavir in 5 ml oral solution	Tablets: No food restrictions Liquid: Take with or after food – Oral solution has high alcohol and propylene glycol content *Caution with disulfiram or metronidazole* *Tablets: store at room temperature Store liquid in refrigerator (stable at <25 °C for 6 weeks)*	Most common: – Diarrhoea, nausea, vomiting, headache, rash, dyslipidaemias – Raised LFTs (esp. AST and ALT) and GGT. More common if hepatitis B or C co-infected – Other protease inhibitor 'class side effects', that is, lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort, carbamazepine* • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases* levels of midazolam – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®) • Caution with erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®) – reduce initial dose (e.g. maximum dose sildenafil 25 mg in 48 h) • *See ritonavir for full list of potential interactions*
Nelfinavir (NFV) Viracept® Roche	1250 mg bd 750 mg tds 250 mg tablets	*Take with or after food to increase bio availability* (up to 2 h after full meal, or with small meal/snack)	Most common: – Diarrhoea and flatulence, nausea Also – Hyperglycaemia/diabetes – Other protease inhibitor 'class side effects', that is, lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort, carbamazepine* • Inhibits CYP450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • *May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban)* • Caution with erectile dysfunction agents sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis) – reduce initial dose (max dose sildenafil 25 mg in 48 h)
Ritonavir (RTV) Norvir ® Abbott	Usually used to 'boost' other protease inhibitors at doses of 100–200 mg od-bd 600 mg bd (antiretroviral dose) 100 mg tablets 400 mg/5 ml oral solution	*Do not administer liquid formulation with disulfiram or metronidazole due to high alcohol content* (tablets ok with metronidazole) Take with or after food if possible (to reduce GI intolerance) *Tablets and liquid stored at room temperature.*	– Asthenia, – Nausea, vomiting, – Diarrhoea, abdominal pain, – Anorexia, – Taste perversion, – Circumoral and peripheral paraesthesiae – Other protease inhibitor 'class side effects', that is, lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – rifampicin contraindicated, *avoid St John's Wort, carbamazepine* • Extremely potent inhibitor of cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with ergotamines, antiarrhythmics, pethidine, piroxicam, amphetamines (inc. ecstasy). Caution with diazepam, antifungals (e.g. ketoconazole), clarithromycin, and carbamazepine* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients or day case attenders (*NB*: Manufacturer advises avoid.) • *Caution with statins – start with lowest dose and titrate according to response. Simvastatin CONTRAINDICATED.*

Continued

Table 41.3 General prescribing points for protease inhibitors—cont'd

Drug, names, manufacturer	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
				• May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • *May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®)* • Caution with erectile dysfunction agents sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra) – reduce initial dose (e.g. maximum dose sildenafil 25 mg in 48 h) • *See BNF/data sheet for full list of contraindications and caution drugs before prescribing*
Saquinavir (SQV) Invirase® Roche	1000 mg (with 100 mg ritonavir) bd Unlicensed doses: – 400 mg (with 400 mg ritonavir) bd – 1600–2000 mg od (with 100 mg ritonavir od) 200 mg capsules, 500 mg tablets	Take with or after food (up to 2 h after a full meal)	– Diarrhoea – Nausea – Abdominal discomfort/wind – Raised LFTs – Prolonged QT interval – Other protease inhibitor 'class side effects', that is, lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort, carbamazepine*. Co-administration of clarithromycin, ketoconazole, ranitidine or cimetidine may increase levels of saquinavir • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders • May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • *May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®)* • Caution with erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra) – reduce initial dose (e.g. max dose sildenafil 25 mg in 48 h) • *If boosted, see ritonavir for full list of potential interactions*
Tipranavir (TPV) Aptivus® *Boehringer Ingelheim*	500 mg bd: co-administer with 200 mg bd ritonavir 250 mg capsules	*Take with or after food to improve GI tolerance* Store in refrigerator (once opened, container may be stored below 30 °C for 60 days)	– Diarrhoea – Nausea, vomiting – Fatigue – Headache – Elevated LFTs – Other protease inhibitor 'class side effects', that is, lipodystrophy syndrome: metabolic/lipid/body shape changes (see BNF for more details)	• Metabolised by cytochrome P450 hepatic enzymes – caution with other drugs which may affect these enzymes – *rifampicin contraindicated, avoid St John's Wort, carbamazepine* • Inhibits cytochrome P450 enzymes. Caution with other drugs metabolised by these enzymes as may get ↑ in levels. *Do NOT co-administer with simvastatin, ergotamines, antiarrhythmics* • *Increases levels of midazolam* – avoid or start with low dose and titrate and monitor carefully; do not use in outpatients, caution in day case attenders (*NB*: Manufacturer advises avoid.) • May increase levels of corticosteroids, including inhaled/intranasal steroids *(avoid fluticasone and budesonide)* • *May require dose alteration of warfarin (monitor INR), methadone, bupropion (Zyban®)* • Caution with erectile dysfunction agents sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®) – reduce initial dose (e.g. maximum dose sildenafil 25 mg in 48 h) • *See ritonavir for full list of potential interactions*

od, once daily; bd, twice daily; e-c, enteric coated; GI, gastro-intestinal; BNF, British National Formulary; LFTs, liver function tests; INR, International normalised ratio; AST, Aspartate transaminase; ALT, alanine transaminase; GGT, γ glutanyl transferase.

Table 41.4 General prescribing points for Integrase Inhibitors

Drug, names, manufacturer	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
Raltegravir Isentress® Merck Sharp and Dohme	400 mg bd 400 mg tablets	Can be taken with or without food	– Nausea, headache – Dizziness, vertigo – Abdominal pain, flatulence, constipation – Pruritus, arthralgia, fatigue – Raised creatine kinase – Myopathy and rhabdomyolysis reported but rare	• *Metabolised by glucuronidation* – caution with potent inducers of this pathway, for example, rifampicin. (No effect on cytochrome P450 enzymes) • Levels increased by proton pump inhibitors – clinical significance uncertain • Levels decreased by ritonavir, tipranavir, efavirenz, St John's Wort, nevirapine, no need for dose adjustment

bd, twice daily.

In addition, there are a number of combination formulations of NRTIs that may be used to reduce pill burden:

Abacavir + lamivudine (Kivexa®)
Tenofovir + emtricitabine (Truvada®)
Zidovudine + lamivudine (Combivir®)
Zidovudine + lamivudine plus abacavir (Trizivir®)

There is also one formulation combining two NRTIs with an NNRTI:
Tenofovir + emtricitabine + efavirenz (Atripla®)

Other triple and quadruple mixed class co-formulations are in development.

Most antiretroviral regimens will include two NRTIs, together with a PI and/or an NNRTI. In the UK, the most commonly prescribed NRTI combination as first-line therapy is tenofovir with emtricitabine (either as the combination formulation Truvada® or, with efavirenz, as Atripla®) which has the benefits of once daily administration and an improved toxicity profile compared to older therapies. A number of combinations should be avoided. These include: zidovudine and stavudine (intracellular competition resulting in antagonism); stavudine and didanosine (unacceptable toxicity); tenofovir and didanosine (unacceptable rates of virological failure and potential for CD4 decline).

Non-nucleoside reverse transcriptase inhibitors

NNRTIs inhibit the reverse transcriptase enzyme by binding to its active site. They do not require prior phosphorylation and can act on cell-free virions as well as infected cells. The NNRTIs available include:

Efavirenz (Sustiva®)
Nevirapine (Viramune®)
Etravirine (Intelence®)

Resistance to NNRTIs occurs rapidly in incompletely suppressive regimens and it is therefore essential that they are prescribed with at least two NRTIs or a combination of NRTIs and PIs. Cross-resistance between nevirapine and efavirenz, which are currently used as first-line NNRTIs, is high. The first of the second-generation NNRTIs, etravirine, is active against some viruses resistant to these agents. Rilpivirine (expected to be licensed in 2011) also has a different resistance profile, but is likely to be used as an alternative first-line NNRTI.

The NNRTIs have much longer plasma half-lives than PIs and NRTIs, so when stopping an NNRTI-containing combination, consideration should be given to either continuing the other agents for a period after cessation of the NNRTI or switching to a boosted PI prior to regimen discontinuation.

Protease inhibitors

PIs bind to the active site of the HIV-1 protease enzyme, preventing the maturation of the newly produced virions so that they remain non-infectious. The following PIs are currently available:

Atazanavir (Reyataz®)
Darunavir (Prezista®)
Fosamprenavir (Telzir®)
Indinavir (Crixivan®)
Lopinavir co-formulated with ritonavir (Kaletra®)
Nelfinavir (Viracept®)
Ritonavir (Norvir®)
Saquinavir (Invirase®)
Tipranavir (Aptivus®)

The use of ritonavir-boosted PIs has superseded use of single PIs, due to better pharmacokinetic profiles, superior efficacy data and reduced likelihood of resistance development. Newer second-generation PIs such as tipranavir and darunavir are effective against many viruses resistant to the earlier PIs. Darunavir is used in first-line PI therapy as a once-daily boosted agent (800 mg with 100 mg of ritonavir); for patients with significant PI resistance a higher dose of 600 mg twice daily, each with ritonavir 100 mg, is used.

Table 41.5 General prescribing points for entry inhibitors

Drug, names, manufacturer, mode of action	Dose and formulation	Administration	Major/common side effects	Significant drug interactions and important pharmacokinetic information
Enfuvirtide (T-20) Fuzeon® Roche Fusion Inhibitor	90 mg bd Ideally every 12 h, but dosing interval of 8–16 h allowed (i.e. 4 h flexibility for each dose) 90 mg/mL powder and solvent for solution for s/c injection Each vial contains 108 mg enfuvirtide, 1 ml of reconstituted solution contains 90 mg enfuvirtide	Single use vials, reconstitute with 1.1 ml water for injection (may take up to 45 min to dissolve powder, DO NOT shake vial) Once reconstituted can be stored in fridge for 24 h (i.e. can make up more than 1 dose at once)	– Injection site reactions very common (pain/discomfort, erythema, nodules/cysts) but not usually requiring discontinuation – Other common side effects; insomnia, headache, lymphadenopathy, eosinophilia – Increased rate of bacterial infections (especially pneumonia) reported – Hypersensitivity reactions requiring discontinuation reported, but rare	• No clinically significant pharmacokinetic interactions expected
Maraviroc Celsentri® ViiV CCR5 Antagonist	Dose varies with co-administered medication: 300 mg bd if not with significant enzyme inhibitors/inducers 150 mg bd with significant enzyme inhibitors (e.g. protease inhibitors) 600 mg bd with significant enzyme inducers (e.g. NNRTIs, rifampicin) 150, 300 mg tablets	Can be taken with or without food. Must only be prescribed for patient with recently confirmed CCR5 tropic virus (i.e. not CXCR4 or dual/mixed tropic virus)	– Nausea most common – Vomiting, abdominal pain, constipation, bloating – Dizziness, paraesthesia, somnolence – Rash – Asthenia – Insomnia – Raised LFTs – Dose limiting adverse reaction in clinical trials, postural hypotension	• *Metabolised* by cytochrome P450 hepatic enzymes, caution with other drugs which may affect these enzymes as dose will *need to be adjusted. Do not co-administer with St John's Wort* • Does not inhibit or induce any cytochrome P450 enzymes • *See product literature for detailed information on dosing* • Adjust dose in renal impairment if co-administered with an enzyme inhibitor (see product literature) • *Contraindicated in patients with peanut or soya allergy (contains soya lecithin)*

bd, twice daily.

An alternative booster to ritonavir, cobicistat, is currently in development and is likely to be co-formulated with PIs as well as elvitegravir (see below).

Entry inhibitors

There are currently two types of entry inhibitors (fusion inhibitors and CCR5 inhibitors) with one agent available in each class. Fusion inhibitors block the structural rearrangement of HIV-1 gp41 and thus stop the fusion of the viral cell membrane with the target cell membrane, preventing viral RNA from entering the cell. CCR5 inhibitors selectively bind to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells.

Enfuvirtide (T-20, Fuzeon®), a fusion inhibitor, is administered subcutaneously and is largely used in heavily treatment experienced patients. The main side effect is injection site reactions. However, following the licensing of new agents from different antiretroviral classes, enfuvirtide is now rarely used.

Maraviroc (Celsentri®), a CCR5 inhibitor, is indicated for use in patients with only CCR5-tropic virus, which is determined by a tropism test just prior to commencing treatment. It is usually used in patients with resistance to one or more other antiretroviral classes.

Integrase inhibitors

Integrase inhibitors bind to the integrase enzyme, thus blocking the integration of viral DNA into host DNA. There is currently one licensed agent, raltegravir (Isentress). Whilst this was initially used in patients with resistant virus, it is increasingly being used either in first-line regimens or where tolerability issues arise with initial therapy. Other agents in development include elvitegravir and dolutegravir. Elvitegravir requires boosting and is being developed as a co-formulation with cobicistat.

Toxicity of antiretroviral therapies

As more antiretroviral agents have become available and the number of patient-years of exposure to them has increased, our understanding of their various toxicities has grown significantly.

Whilst there are many individual drug toxicities (see Tables 41.1–41.5), there are also a number of class-specific or therapy-related toxicities (Carr and Cooper, 2000).

Mitochondrial toxicity. Mitochondrial toxicity is increasingly recognised in patients with prolonged exposure to nucleoside analogue antiretrovirals, particularly stavudine, didanosine and, to a lesser extent, zidovudine, and is thought to explain such side effects as peripheral neuropathy, myopathy, pancreatitis and lactic acidosis. If these problems should arise, management is to switch the likely causative agent, if possible (McComsey and Lonergan, 2004).

Rash and hepatitis. These are both recognised side effects of the NNRTI class, although the incidence and severity appear greatest with nevirapine, particularly in patients with a higher CD4 count (>250 cells/mm^3 for women and >400 cells/mm^3 for men). Management is either close observation (in mild-to-moderate cases) or withdrawal of the causative agent (in severe cases). An abacavir hypersensitivity reaction is well characterised and historically occurs in approximately 6–8% of individuals who receive abacavir. It typically presents in the first 6 weeks of therapy as a progressive illness with fevers, rash and flu-like symptoms. Fatalities have been reported where the drug has subsequently been reintroduced in patients with a prior history of hypersensitivity reaction. Management has traditionally been to withdraw the agent and never reintroduce. However, the use of newer pharmacogenomic techniques, for example, HLA B*5701 testing, and subsequent prescription of abacavir only to those who are B*5701 negative have dramatically reduced the incidence of hypersensitivity reaction (Mallal et al., 2008).

Lipodystrophy. Lipodystrophy has been well reported in individuals on HAART. This is characterised by one or both of lipoatrophy (fat loss, particularly from the face, upper limbs and buttocks) and lipohypertrophy (abnormal fat deposition, particularly affecting the abdomen and neck). Whilst these body shape changes are associated with drug therapy, predominantly stavudine and zidovudine for lipoatrophy and possibly PIs for lipohypertrophy, it is likely that host and disease factors also play a role in aetiology (Carr, 2003; Lichtenstein, 2005). Management at present is to avoid or switch away from the causative agent(s) and/or to use cosmetic approaches (fillers or liposuction). Since the decline in use of the older NRTIs, the incidence of lipodystrophy has decreased dramatically.

Metabolic disturbances. Hypercholesterolaemia and hypertriglyceridaemia, in particular, are frequently seen in patients receiving HAART. Again, the aetiology of these toxicities is likely to represent a combination of drug and host factors. However, they are particularly associated with PIs, although the incidence appears lower with atazanavir. Whilst it is likely that this hyperlipidaemia contributes to an increased cardiovascular disease risk, this needs to be considered in the context of traditional risk factors, for example, smoking, which may be present in this patient group. Management is to reduce all modifiable risk factors and either switch away from the likely causative agent to one more metabolically favourable or consider adjunctive lipid-lowering therapy, taking into consideration potential drug–drug interactions (Schambelan et al., 2002).

Renal impairment and, rarely, Fanconi's syndrome have been reported with tenofovir. Creatinine clearance should be calculated and proteinuria quantified prior to starting therapy with this agent and should be monitored regularly.

Cardiovascular disease. Cohort studies have suggested an increased risk of cardiovascular disease with some PIs (Kaletra® and indinavir) and with the NRTI, abacavir (Sabin et al., 2008; Worm et al., 2010). This risk is independent of the effect on lipids and the mechanism has yet to be determined. As with lipid disturbances, the decision to start or continue these agents needs to be considered as part of a holistic approach to cardiovascular risk.

Opportunistic infections and malignancies

Detailed information on treatment guidelines can be obtained by consulting the relevant national guidelines, for example, British HIV Association guidelines for the management of opportunistic infections (Nelson et al., 2010),

tuberculosis (Pozniak et al., 2010), malignancies (Bower et al., 2008). Dosing schedules for the most commonly used drugs used to treat opportunistic infections are summarised in Table 41.6.

Fungal infections

***P. jiroveci* pneumonia.** This remains one of the most common causes of morbidity and mortality in HIV-positive individuals. Classically, patients present with an insidious onset of a non-productive cough, shortness of breath on exertion and an inability to take a deep breath. Fever, anorexia and weight loss are common accompanying symptoms. Patients are usually markedly immunosuppressed, with CD4 counts less than 200 cells/mm^3. Diagnosis is supported by the presence of exercise-induced oxygen desaturation and the typical chest radiographic appearance of bilateral interstitial shadowing, though in mild cases, the chest X-ray may be normal. *P. jiroveci* cannot be cultured in vitro, so the diagnosis is confirmed by demonstration of the organism by immunofluorescence or silver staining, or by nucleic acid amplification techniques (NAAT), of samples obtained by bronchoalveolar lavage. Sputum induction, by nebulisation of hypertonic sodium chloride, is not recommended for obtaining samples unless the procedure is being performed in the treatment centre sufficiently regularly to enable staff to maintain competence, as diagnostic sensitivity of the test is significantly affected by technique.

Treatment is instigated in patients with a proven diagnosis, or empirically where there is a suspicion prior to confirmation. Adequate samples may be obtained to make a diagnosis up to 7–10 days after starting treatment. Oxygen is essential for patients with compromised respiratory function. First-line therapy is high-dose co-trimoxazole for 21 days: oral for mild cases (1920 mg three times daily), and intravenous for moderate-to-severe disease (120 mg/kg/day in divided doses for 3 days, then 90 mg/kg/day for 18 days). Nausea and vomiting commonly occur and may be best managed pre-emptively by administration of a prophylactic antiemetic.

In cases of co-trimoxazole intolerance, several alternative therapies are available. For mild *P. jiroveci* pneumonia, a combination of oral trimethoprim (10–15 mg/kg/day in two divided doses) with dapsone (100 mg daily) may be effective. For moderate-to-severe disease, a combination of clindamycin (intravenous or oral) and primaquine is often used. Intravenous pentamidine is another alternative, though its use may be associated with more significant adverse reactions. Pentamidine should also be given in nebulised form (600 mg) via a suitable nebuliser, for example, Respirgard II, for the first 3 days, to ensure prompt attainment of adequate lung tissue levels. Oral atovaquone suspension can be used for mild-to-moderate *P. jiroveci* pneumonia but must be taken with food, particularly fatty food, to be effective. Glucose-6-phosphate dehydrogenase (G6PD) levels should be checked prior to (or as soon as possible after starting) treatment with co-trimoxazole, dapsone or primaquine.

For cases of moderate-to-severe *P. jiroveci* pneumonia (PaO_2 < 9.3 kPa or SpO_2 < 92%), adjunctive corticosteroid therapy is recommended, for example, prednisolone 75 mg daily for 5 days, 50 mg for 5 days, and then 25 mg for 5 days. Ventilatory support should be considered for patients in whom the underlying prognosis is good, for example, those presenting for the first time with *P. jiroveci* pneumonia, those without severe co-existing medical complications and those with remaining effective antiretroviral options.

It has been clearly demonstrated that prophylactic therapy reduces both the incidence and severity of *P. jiroveci* pneumonia in patients with either prior disease or those at risk of a first episode, and that this intervention significantly improves survival. Primary prophylaxis is recommended for those individuals with a previous AIDS-defining illness, markedly symptomatic disease (including oral candidiasis), a CD4 count < 200 cells/mm^3 or CD4 percentage <14%. Prophylaxis can be discontinued when CD4 is sustained above 200 cells/mm^3 for over 3 months on HAART.

Co-trimoxazole is the gold standard and also confers protection against toxoplasmosis and some other bacterial infections. Commonly used regimens with proven efficacy are 960 mg daily or three times a week or 480 mg daily. The incidence of adverse reactions to co-trimoxazole in HIV-positive individuals is higher than in the general population, although many patients who are intolerant of high-dose treatment do not experience problems at prophylactic doses. In cases of intolerance, several alternative approaches may be adopted. Desensitisation may be attempted or other agents may be used. Dapsone 100 mg daily, with or without pyrimethamine, according to *Toxoplasma* status, is effective but does not offer such broad protection against bacterial infections. Nebulised pentamidine at a dose of 300 mg every month via an appropriate nebuliser (with prior nebulised or inhaled β_2-agonist to prevent bronchospasm) can also be used but does not protect against extra-pulmonary *P. jiroveci* pneumonia.

Oropharyngeal candidiasis. Candidiasis is a frequent manifestation of HIV infection and may occur early in the disease. Clinically, it is usually characterised by white plaques on the oral mucosa, but may present as erythematous patches or as angular cheilitis. If swallowing is difficult (dysphagia) or painful (odynophagia), oesophageal involvement may be suspected.

First-line therapy for oral candidiasis is a systemic agent, usually fluconazole (50 mg daily for 7 days). An alternative is itraconazole (200 mg once daily); the solution has higher bioavailability than the capsule formulation and does not require an acid pH for absorption. Topical therapies are available where there is a clinical decision to avoid systemic antifungals (e.g. in patients with hepatic failure). They are as effective as oral azoles for oropharyngeal disease, but time to yeast clearance is longer and relapse rate is higher.

In cases of oesophageal candida, which is an AIDS-defining illness, systemic therapy is necessary using higher doses of the above agents for a longer duration, for example, fluconazole 100 mg once daily for 2 weeks. Continuous azole therapy or frequent courses of these drugs predispose to the development

Table 41.6 Selected drugs to treat opportunistic infections in HIV disease

Drug	Indication	Dosage: route, frequency, duration	Common or significant side effects include:	Significant interactions	Monitoring	Comments
Aciclovir	Herpes simplex Herpes zoster Prophylaxis/ suppression of herpes infections	5–10 mg/kg i.v. three times daily for 5–10 days, 200–400 mg p.o. five times daily for 5–10 days, 10 mg/kg i.v. three times daily for 5–10 days, 800 mg p.o. five times daily for 7 days. 200–400 mg p.o. twice daily	Nausea, vomiting, abdominal pain, diarrhoea, skin rash, abnormal LFTs extravasation (i.v.), renal impairment (i.v.). Confusion and other CNS effects (i.v.). Rapid increases in blood urea and creatinine levels related to peak plasma levels and the state of hydration of the patient	Ciclosporin, mycophenolate mofetil, tacrolimus, probenecid, lithium, theophyline, nephrotoxic drugs	Renal function (with i.v.)	Higher dose and longer duration for herpes encephalitis or varicella zoster. Patients on HAART with CD4 >300 cells/ mm^3 may be treated as for immunocompetent. Intravenous infusion diluted to 0.5% (w/v) and infused over at least 1 h (reduces likelihood of renal toxicity)
Amphotericin 1. Sodium deoxycholate (Fungizone®) 2. Liposomal (AmBisome®) 3. Lipid complex (Abelcet®)	Cryptococcal meningitis and other severe fungal infections	Test dose of 1 mg i.v. (over 10–30 min, depending on product), followed by once daily i.v.: 1. 0.25–1.0 mg/kg (increased over 3–5 days as tolerated) 2. 1–3.0 mg/kg (increased over 2–3 days) 3. 5 mg/kg. Duration: 2–6 weeks (total induction period at least 6 weeks)	Fever, chills, nausea and vomiting, headache, anorexia, weight loss, malaise, myalgia, thrombophlebitis, epigastric pain, diarrhoea, renal impairment; hypokalaemia, hypomagnesaemia, anaemia hypotension, vasodilatation, flushing, liver function tests abnormal, hyperbilirubinaemia, alkaline phosphatase increased	Nephrotoxic drugs, antineoplastics, corticosteroids	Renal function, FBC, U+Es	Test dose required before first infusion with any parenteral amphotericin. All i.v. preparations administered in 5% glucose. Pre-and post-hydration with 0.9% sodium chloride may decrease nephrotoxicity. Liposomal and lipid complex formulations generally better tolerated
Atovaquone Suspension	Treatment of mild-moderate PCP Prophylaxis of PCP[a] Treatment of toxoplasmosis[a]	750 mg p.o. twice daily with food for 3 weeks 1.5 g p.o. twice daily for at least 6 weeks	Nausea, rash, diarrhoea, vomiting, headache, insomnia, fever, increased LFTs, decreased sodium, anaemia, neutropenia. Hyponatraemia, hypersensitivity reactions including angioedema, bronchospasm and throat tightness	Indinavir, metoclopramide, rifampicin, rifabutin, tetracycline	LFTs, U+Es, FBC	Absorption improved by taking with food (especially high fat food); reduced by diarrhoea
Azithromycin	Atypical *Mycobacterium* infections, toxoplasmosis and PCP (adjunctive therapy or part of combination regimen) MAC prophylaxis	500 mg oral daily for MAI treatment or PCP prophylaxis; 1250 mg oral once weekly for MAI prophylaxis[b]; 1250 mg daily for toxoplasmosis treatment[b]	Nausea, vomiting, abdominal discomfort, anorexia, dyspepsia, flatulence, diarrhoea, constipation, raised LFTs. (rare: ototoxicity)	Antacids, theophylline, coumarins, ciclosporin artemether/ lumefantrine, ergot derivatives, digoxin, bromocriptine, cabergoline, reboxetine, oestrogens	LFTs, hearing (if on long-term or high-dose therapy)	Less significant drug interactions than with the other macrolides For patients allergic to soya or peanut: risk of hypersensitivity reactions with some formulations and brands

Continued

Table 41.6 Selected drugs to treat opportunistic infections in HIV disease

Drug	Indication	Dosage: route, frequency, duration	Common or significant side effects include:	Significant interactions	Monitoring	Comments
Cidofovir	Cytomegalovirus retinitis	5 mg/kg weekly for two doses, then every 2 weeks thereafter	Renal impairment, neutropenia, ocular hypotony, iritis/uveitis, nausea, vomiting, alopecia, rash, asthenia, fever, chills, headache	Other nephrotoxic drugs, agents that are contraindicated with probenecid, tenofovir	Renal function (including urine protein) neutrophils	Must be co-administered with probenecid and intravenous fluids (see SPC/BNF for specific regimen). Caution with handling (potential carcinogen). Avoid if on tenofovir
Clindamycin	Treatment of PCP Toxoplasmosis treatment Toxoplasmosis maintenance	600 mg i.v./p.o. four times daily for 3 weeks 600 mg i.v./p.o. four times daily for at least 6 weeks 1.2 g p.o. daily in 3–4 divided doses	Diarrhoea, abdominal discomfort, oesophagitis, nausea, vomiting, rash, abnormal LFTs, thrombophlebitis (i.v.). Rarely pseudomembranous colitis, blood dyscrasias	Non-depolarising muscle relaxants, suxamethonium, oestrogens, pyrido-stigmine, neostigmine, erythromycin	LFTs, renal function, FBC, diarrhoea	Taken with primaquine for PCP. Taken with pyrimethamine for toxoplasmosis. Higher doses may be used if previous failure of co-trimoxazole (for PCP) or sulfadiazine (for toxoplasmosis)[b]
Co-trimoxazole (trimethoprim + sulpha-methoxazole)	Treatment of PCP Prophylaxis of PCP	Moderate–severe: 120 mg/kg i.v in 2–4 divided doses for 3 days, then 90 mg/kg for 18 days; mild: 1920mg p.o. three times daily for 3 weeks. Prophylaxis: 480 or 960mg p.o. daily or 960mg three times per week (960mg daily if on rifampicin)	Nausea, diarrhoea, headache, rash, hyperkalaemia, vomiting. (rare: drug fever, blood dyscrasias, serious skin reactions, e.g. Stevens-Johnson syndrome)	Amiodarone, oestrogens pyrimethamine, rifampicin, ciclosporin, lamivudine phenytoin, azathioprine, mercaptopurine, metho-trexate, sulphonylureas, warfarin	FBC, renal function, LFTs rash	For infusion, dilute each 480 mg with 125 ml of glucose 5% or sodium chloride 0.9% and infuse over 1.5–3 h. If fluid restricted, 480 mg in 75 ml of glucose 5%. Caution in G6PD deficiency
Dapsone	Prophylaxis of PCP Treatment of PCP[a]	100 mg p.o. daily (with trimethoprim 10–15 mg/kg/day in divided doses for 3 weeks for PCP treatment)	Anorexia, nausea, vomiting, rash. (rare: blood dyscrasias including methaemoglobinaemia; dapsone syndrome)	Rifamycins, probenecid, oestrogens, antacids	FBC, LFTs	Caution in G6PD deficiency
Famciclovir	Treatment of herpes zoster. Treatment of genital herpes	Doses for immunocompromised patients: zoster use 500 mg three times daily for 10 days; genital herpes all episodes use 500 mg twice daily for 7 days, for suppression 500 mg twice daily	Headache, nausea, diarrhoea, vomiting, abdominal pain, constipation, increased tendency to sweat, pruritus	Probenecid	Renal function	Patients on HAART with CD4 >300 cells/mm^3 may be treated as for immunocompetent
Fluconazole	Oesophageal candidiasis Oropharyngeal candidiasis Cryptococcal meningitis treatment Cryptococcal meningitis prophylaxis	100 mg p.o. daily for 2 weeks 50 mg p.o. daily for 7–14 days 400 mg i.v./p.o. daily for ≥8 weeks 200 mg p.o. daily	Headache, rash, abdominal pain, diarrhoea, flatulence, nausea, abnormal LFTs, hepatotoxicity	Coumarins, midazolam, sulphonylureas, rifabutin, rifampicin, phenytoin, tacrolimus, ciclosporin, theophylline, zidovudine, terfenadine	Renal function LFTs	Higher doses have been used for treatment and prophylaxis of candida and cryptococcus infections (depending on clinical response and antifungal sensitivities) i.v. route only necessary if patient nil by mouth.

Flucytosine	Cryptococcal meningitis treatment	100 mg/kg daily p.o./i.v. in four divided doses for 2 weeks (with i.v. amphotericin)	Nausea, vomiting, diarrhoea, rash (rare: blood dyscrasias, hepatotoxicity)	Cytarabine	Renal function FBC, LFTs	Oral formulation is no longer licensed in the UK but can be imported on named-patient basis
Foscarnet	Cytomegalovirus retinitis treatment Cytomegalovirus retinitis maintenance	180 mg/kg/day i.v. in 2–3 divided doses (adjust according to renal function) over 2 h for 3 weeks 60, 120 mg/kg i.v. once daily over 2 h for 5–7 days each week	Renal impairment, alterations in serum calcium, potassium, magnesium and other minerals, headache, rash, convulsions, thrombophlebitis, genital ulceration, anaemia, nausea, vomiting, diarrhoea, paraesthesia	Nephrotoxic drugs, drugs that inhibit renal tubular secretion (e.g. probenecid), i.v. pentamidine. When diuretics are indicated, thiazides are recommended	Renal function, LFTs, serum magnesium, potassium, calcium and phosphate, FBC, U+Es	Good hydration, prompt correction of electrolyte abnormalities and dose adjustment for renal function vital. Wash genital area after micturition to reduce risk of ulceration. Give centrally to prevent phlebitis. If infusion related side effects reduce rate. Adjust maintenance dose for disease state, drug tolerability and renal function
Ganciclovir	Cytomegalovirus induction treatment Cytomegalovirus retinitis maintenance	5 mg/kg i.v. twice daily for 3 weeks, 5 mg/kg i.v. once every day or 6 mg/kg once daily for 5 days each week	Blood dyscrasias, anorexia, renal impairment, abnormal LFTs, central nervous system effects, fatigue, nausea, vomiting, flatulence, abdominal pain, dysphagia, dysgeusia, dyspepsia, constipation, ear pain, injection site reactions, eye disorders and skin disorders	Zidovudine, didanosine, imipenem-cilastatin, probenecid, mycophenolate mofetil, nephrotoxic drugs, bone marrow suppressive agents	FBC renal function, LFTs	Give over 1 h preferably via central venous access Caution with handling. Special dosage instructions for patients with renal impairment: Women of child bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter
Peginterferon alfa	Hepatitis C (in combination with ribavirin) Chronic hepatitis B	See product literature for dose and duration (varies by brand, genotype and initial response) weekly s.c. injection	Severe CNS and psychiatric effects, anorexia, nausea, influenza-like symptoms, lethargy, depression, ocular side effects, rash, myelosuppression, hypertriglyceridaemia	Theophylline	Lipids, renal function, LFTs, TFTs, U+Es, FBC, blood glucose	Longer duration of treatment in HIV-coinfected patients. Should be managed jointly by HIV and hepatology specialists
Pentamidine isetionate	PCP treatment Mild PCP treatment PCP prophylaxis	4 mg/kg i.v. once daily for 3 weeks (+600 mg nebulised for first 3 days) 600 mg nebulised daily for 3 weeks 300 mg nebulised every 4 weeks	Intravenous: renal impairment, postural hypotension, leucopenia, hypo/hyperglycaemia, pancreatitis, electrolyte disturbances, nausea, vomiting. Nebulised: cough, bronchospasm	Nephrotoxic drugs, foscarnet, drugs that prolong QT interval (e.g. quinolones, erythromycin)	Renal function, blood glucose, blood pressure, U+Es	Infuse over 1 h with patient supine. Caution with handling. Pretreat with bronchodilator if nebulised and use special nebuliser
Primaquine	PCP treatment	15–30 mg p.o. daily for 3 weeks	Nausea, vomiting, anorexia, abdominal pain (rare: methaemoglobinaemia, haemolytic anaemia)	Bone marrow suppressive drugs, artemether/lumefantrine	FBC	Avoid in G6PD deficiency

Continued

Table 41.6 Selected drugs to treat opportunistic infections in HIV disease

Drug	Indication	Dosage: route, frequency, duration	Common or significant side effects include:	Significant interactions	Monitoring	Comments
Pyrimethamine	Toxoplasmosis treatment Toxoplasmosis maintenance	100 mg on day 1, then 50 mg p.o. once daily for at least 6 weeks Different in SPC 25 mg p.o. once daily	Anaemia, leucopenia, thrombocytopenia, rash	Bone marrow suppressive drugs, anti-malarials, methotrexate, antacids, lorazepam, kaolin, highly protein-bound drugs (e.g. coumarins)	FBC	Combined with sulfadiazine or clindamycin. Higher dose can be used if previous treatment failure Recommend folinic acid 15 mg od to reduce bone marrow suppression
Ribavirin	Hepatitis C treatment	Dose depends on product (Copegus or Rebetol), weight and hepatitis C genotype, see SPCs for specific details	Anaemia, neutropenia, thrombocytopenia. For other side effects reported in combination with peginterferon alfa, see earlier entry	Stavudine, zidovudine, didanosine, abacavir	FBC, LFTs, renal function	Given with peginterferon alfa Colony stimulating factor support may counteract haematological side effects without requiring dose reduction. Teratogenic
Rifabutin	MAI prophylaxis MAI treatment	300, 450 mg p.o. once daily with other drugs (consult SPC for specific details) 150 mg 3 times a week with Kaletra[b]	Abnormal LFTs, nausea, vomiting, bone marrow suppression, arthralgia, myalgia, jaundice (rare: uveitis, risk increased with concomitant administration of drugs that increase rifabutin levels)	Coumarins, aripiprazole, atovaquone, dapsone, efavirenz, erythromycin, clarithromycin, protease inhibitors, sirolimus, oral hypoglycaemics, azole and triazole antifungals, disopyramide, quinidine, carbamazepine, oestrogens, progestogens	LFTs, renal function	Combine with at least one other drug for MAI treatment. TDM of both agents may be useful when given with Kaletra
Sulfadiazine	Toxoplasmosis treatment[a] Toxoplasmosis maintenance[a]	1–1.5 g i.v./p.o. four times daily for at least 6 weeks. 2 g p.o. daily in divided doses	Nausea, vomiting, rash, bone marrow suppression, crystalluria (and see under co-tri moxazole)	Bone marrow suppressive drugs, ciclosporin, oestrogens, coumarins, methenamine	Renal function, LFTs, FBC	Use with pyrimethamine. Prevent crystalluria by ensuring good fluid input/output. Alkalinising urine with sodium bicarbonate may help if crystals formed
Valaciclovir	Herpes zoster treatment Herpes simplex treatment	1 g p.o. three times daily for 7 days. 500 mg p.o. twice daily for 5–10 days (initial) or 5 days (recurrent) episodes	Mild headache and nausea (more serious events reported in transplant patients on 8 g/day long term)	Ciclosporin mycophenolate mofetil tacrolimus probenecid	Renal function	Interactions more likely to be significant if renal impairment
Valganciclovir	CMV retinitis	Induction treatment: 900 mg twice a day with food for 3 weeks Maintenance: 900 mg once daily with food	See ganciclovir, similar potential side effects (except those associated with intravenous administration, e.g. injection site reactions)	As for ganciclovir	FBC, renal function, LFTs	

FBC, full blood count; U+Es, urea and electrolyte levels; LFTs, liver function tests; TFTs, thyroid function tests; MAI, *Mycobacterium avium intracellulare*; G6PD, glucose-6-phosphate dehydrogenase; PCP, *Pneumocystis jiroveci* pneumonia; CMV, cytomegalovirus; p.o., oral; i.v., intravenous; s.c., subcutaneous; SPC, Summary of product characteristics; BNF, British National Formulary; w/v, weight/volume; TDM, therapeutic drug monitoring; MAC, *Mycobacterium avium* complex.

[a]Unlicensed treatment indication in UK.

[b]Unlicensed dose in UK.

of azole resistance. In such instances, an alternative azole or an echinocandin may be used, or occasionally higher than usual doses of the original agent, for example, fluconazole 400 mg daily. In intractable cases, intravenous amphotericin may be required. With the use of HAART, such complications are rarely seen.

Cryptococcus neoformans. This causes a disseminated infection, usually with meningeal involvement, in individuals with HIV infection. Patients present with fever and headaches, often without the characteristic symptoms of meningism such as photophobia and neck stiffness. Diagnosis is normally made on the basis of CSF analysis, though serum cryptococcal antigen and blood cultures may also be indicative.

For patients who are moderately or severely unwell, intravenous amphotericin B deoxycholate (0.7–1 mg/kg/day) or a lipid complex/liposomal formulation, with or without flucytosine (100 mg/kg/day in divided doses, oral or intravenous) is the first-line therapy. The place of flucytosine in therapy remains uncertain, with the only clear benefit seen in patients not on HAART, in whom it speeds the rate of CSF sterilisation and reduces the relapse rate. However, it has not been shown to reduce mortality and can be associated with additional toxicity. Conventional amphotericin is associated with high rates of nephrotoxicity, leading in some cases to acute renal failure and death, although strategies can be employed to minimise adverse effects. However, despite the higher cost, the liposomal form (AmBisome®, 4 mg/kg/day) is now usually the agent of choice due to its more favourable toxicity profile. Many UK hospitals now only stock one intravenous amphotericin product, due to reports of errors following confusion between different formulations because doses, reconstitution procedures and administration vary. The usual duration of amphotericin (± flucytosine) treatment is 2 weeks, after which high-dose fluconazole (400 mg daily orally) should be continued for further 10 weeks. Subsequent maintenance therapy with fluconazole 200 mg daily has been shown to be effective in reducing the incidence of relapse and should be continued for life, or until immune function is restored (for example, CD4 > 100 cells/mm^3 in the presence of an undetectable viral load for at least 3 months). In milder cases fluconazole may be given for the entire duration of treatment. Itraconazole (400 mg/day) has been used but is less effective than fluconazole and should be used only if other agents are contraindicated.

Protozoal infections

Toxoplasmosis. *T. gondii* is a frequent cause of central nervous system disease in patients with AIDS. Individuals may present with headaches, fever, confusion, seizures or focal neurological symptoms and signs. Diagnosis is usually based on the appearance of ring-enhancing lesion(s) on computed tomography (CT scan). Definitive diagnosis is based on brain biopsy, which is rarely performed, but is generally made presumptively after response to therapy.

First-line treatment is sulphadiazine and pyrimethamine, with folinic acid to prevent myelosuppression, for 6 weeks, followed by maintenance therapy with lower doses of the same agents until CD4 count is consistently maintained above 200 cells/mm^3. The preferred alternative is clindamycin and pyrimethamine with folinic acid, with limited data for atovaquone, co-trimoxazole, clarithromycin and doxycycline. Adjunctive therapy with corticosteroids or anticonvulsants may be used in cases of severe oedema or seizures, respectively.

Cryptosporidiosis. *Cryptosporidium parvum* is a ubiquitous organism and a common cause of diarrhoea in immunocompetent individuals. In patients who are immunocompromised, persistent infection may occur characterised by abdominal pain, weight loss and severe diarrhoea. Diagnosis is generally based on stool analysis.

Although many agents have been investigated for the treatment of cryptosporidiosis, the majority of results have been disappointing. Nitazoxanide is possibly the most promising agent, but failed to demonstrate superiority over placebo in severely immunocompromised patients. The optimal treatment for cryptosporidiosis (and indeed the majority of chronic opportunistic infections) is to increase immunological function with HAART. The mainstay of management in patients who are not able or willing to take HAART remains symptomatic control with nutritional supplementation, adequate hydration and antidiarrhoeal agents.

Bacterial infections

Bacterial infections are common in the context of HIV infection. Recurrent bacterial pneumonia, particularly *Streptococcus pneumoniae,* and diarrhoeal illnesses associated with *Salmonella, Shigella* or *Campylobacter* are particularly common. In general, these are treated the same as in immunocompetent individuals, although recurrent infections and/or septicaemia occur more frequently.

Mycobacteria. In HIV-positive individuals, *M. tuberculosis* (TB) is characterised by increased likelihood of reactivation of latent disease; more rapid progression to clinical disease following acquisition; more frequent extrapulmonary manifestations of tuberculosis; and more rapid progression of HIV disease (if the individual is not receiving HAART). Overall, there is no increase in infectivity of tuberculosis compared with HIV-negative patients.

Definitive diagnosis is reliant on culture of the organism from biological specimens but may be complicated by atypical clinical features and reduced response to tuberculin testing; it is often necessary to initiate treatment empirically.

Treatment for pulmonary and extrapulmonary tuberculosis should follow conventional guidelines for immunocompetent individuals. Meningitis is an unusual but significant complication of tuberculosis. Treatment for all forms of CNS tuberculosis should consist of four drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) for 2 months followed by two drugs (isoniazid, rifampicin) for at least 10 months. Adjunctive corticosteroids (either dexamethasone or prednisolone) should be given to all patients with tuberculous meningitis, regardless of disease severity (Thwaites et al., 2009).

The use of primary and secondary prophylaxis remains controversial but may be appropriate in high-incidence groups. The increased incidence of multidrug-resistant tuberculosis (MDRTB) and the emergence of extremely drug-resistant disease (XDRTB) is a cause for concern and raises many infection control issues. It also highlights the need for antibiotic therapy driven by bacteriological sensitivities.

Managing tuberculosis and HIV co-infection is further complicated by drug–drug interactions between antituberculous and antiretroviral agents, overlapping toxicities and the risk of development of immune reconstitution disease (see later). This is a complex area and treatment should be guided by clinicians with the relevant specialist expertise (Pozniak et al., 2010). One of the most frequent concerns is when to initiate therapy for HIV in an individual receiving TB treatment. This decision is based upon the risk of developing other opportunistic infections in the medium term. HAART is usually started after 2 weeks of tuberculosis treatment in those with severe immunosuppression (CD4 <100 cells/mm^3), after 2 months if the CD4 is between 100 and 200 cells/mm^3, and on completion of tuberculosis treatment or at 6 months if the CD4 is greater than 200 cells/mm^3.

M. avium intracellulare (MAI) or *M. avium* complex (MAC) infection was historically a frequent manifestation of late-stage HIV disease, but is rarely seen now that HAART is widely used. Patients with disseminated infection classically present with fevers, weight loss, diarrhoea and hepatosplenomegaly. Diagnosis is sometimes made presumptively but is usually based on culture of the organism(s). *In vitro* sensitivities may not be good predictors of response to therapy. Therapy may need to be tailored to account for drug interactions with concomitant antiretrovirals, but usually includes azithromycin and ethambutol (ideally with rifabutin). Alternative agents include the quinolones and amikacin. Corticosteroids may be useful for symptomatic control. Although rifabutin, clarithromycin and azithromycin have all been demonstrated to be effective agents for primary prophylaxis against MAI, their cost–benefit remains controversial and use is not widespread in the UK. The strongest indications are for those patients with CD4 <50 cells/mm^3 who decline HAART, or who experience HAART failure (without further effective options) or who are receiving chemotherapy.

Viral infections

Cytomegalovirus. CMV is a herpes virus that is acquired by approximately 50% of the general population and over 90% of homosexual men. Like other herpes viruses, once infection has occurred, the virus remains dormant thereafter, but in individuals with advanced immunosuppression, reactivation may occur and cause disease. In the context of HIV infection, the most common sites of disease are the retina and gastrointestinal tract, though neurological involvement and pneumonitis are well reported.

Diagnosis of CMV retinitis is based on clinical appearance; it may be detected in asymptomatic individuals but usually presents with symptoms of blurred vision, visual field defects or 'floaters'. Untreated CMV retinitis progresses rapidly to blindness and treatment substantially reduces the morbidity associated with this condition. Although previously lifelong treatment had been recommended, where immunological restoration occurs discontinuation may be possible. Conventional therapeutic approaches are based upon an initial induction period of high-dose therapy for 2–3 weeks, until the retinitis is quiescent, followed by lower dose maintenance treatment, with reinduction if disease progression occurs.

The most commonly used agent for induction therapy in the UK is ganciclovir, which can be given intravenously or orally, as the pro-drug valganciclovir. It is usually administered (5 mg/kg) via a central line over 1 h and should be handled as a cytotoxic agent. Valganciclovir is well absorbed and a dose of 900 mg twice daily has been shown to be as effective as intravenous ganciclovir for induction therapy. Significant side effects encountered with these agents include neutropenia, which may require colony-stimulating factor support, and thrombocytopenia. Maintenance treatment may also be given either intravenously (6 mg/kg on 5 days a week) or orally (valganciclovir 900 mg once daily).

Intravenous maintenance therapy requires the insertion of a permanent indwelling catheter and is therefore usually used only when oral administration is not possible. Intravitreal administration of ganciclovir is possible, but rarely used, as this does not confer any systemic protection.

An alternative agent to ganciclovir is foscarnet. It has a less favourable toxicity profile and is thus usually reserved for cases of therapeutic failure with ganciclovir. Its main adverse effects are electrolyte abnormalities, nephrotoxicity that requires dose adjustment or cessation of therapy, and ulceration, particularly of the genitals, which may be prevented by assiduous attention to personal hygiene after micturition. No effective oral formulation is currently available.

Cidofovir requires less frequent administration: two doses at weekly intervals for induction and fortnightly for maintenance, though intravenous administration is again required and nephrotoxicity and other metabolic disturbances are well recognised. A strict regimen of intravenous hydration and oral probenecid (2 g given 3 h prior to infusion and 1 g 2 and 8 h post-cidofovir) must be followed. The risk of nephrotoxicity is increased if cidofovir is co-administered with agents such as tenofovir that are excreted via the same renal tubular anion transporter.

CMV disease of the gastro-intestinal tract usually affects the oesophagus or colon, causing dysphagia and abdominal pain with diarrhoea, respectively. Diagnosis is based upon histological analysis of biopsy specimens. Treatment is as for CMV retinitis induction therapy; maintenance therapy is not usually given unless relapses occur. Neurological disease may present in a variety of ways, is difficult to diagnose and frequently carries a poor prognosis, even with treatment. The optimal agent, dosage and duration of therapy remain undetermined.

Impact of HAART on opportunistic infections

The widespread use of HAART has had a dramatic effect on the incidence, prognosis and clinical aspects of opportunistic infections.

Decreased incidence of opportunistic infections. HAART has resulted in a major reduction in the vast majority of opportunistic infections and a consequent reduction in mortality rates and requirement for hospital admissions.

Withdrawal of prophylaxis. The rise in CD4 count associated with HAART has led to an improvement in functional immunity. Clinical trials have suggested that the withdrawal of both primary and secondary prophylaxis against *P. jiroveci* pneumonia is safe, and similar results are thought to be likely for cryptococcosis, toxoplasmosis, MAI and CMV. Most would consider withdrawing prophylaxis in individuals on successful HAART if the CD4 count is consistently greater than 200 cells/mm^3 (*P. jiroveci* pneumonia, toxoplasmosis, cryptococcosis) or 100 cells/mm^3 (MAI and CMV).

Successful treatment of opportunistic infections. Some previously difficult to treat infections, notably cryptosporidiosis and microsporidiosis, appear to resolve with significant CD4 count improvements associated with HAART. However, in up to 30% of individuals, initiation of HAART can be associated with a clinical deterioration known as immune reconstitution inflammatory syndrome or IRIS. This typically occurs in the first 2–6 weeks after starting HAART and presents as fevers and localised symptoms pertaining to a recently treated or previously undiagnosed opportunistic pathogen. It is most frequently seen with mycobacteria (lymphadenitis with both *M. tuberculosis* and MAI) and CMV (vitritis, iritis and retinal oedema), but has been reported for most infections. Diagnosis is difficult as the signs and symptoms mimic those of resistant disease, non-adherence and co-morbidity. No management strategy is proven but corticosteroids, NSAIDs and immunomodulatory therapies (IL-2 and GM-CSF) have all been used.

Cancers

Although there are a number of malignancies associated with HIV infection, the most common are Kaposi's sarcoma and lymphoma.

Kaposi's sarcoma. This is the most common malignancy in people with HIV infection and may be triggered by infection with human herpes virus 8 (HHV-8). The majority of lesions affect the skin and appear as raised purple papules. These may be single or multiple and in severe cases may result in oedema, ulceration and infection. Visceral involvement is not uncommon but rarely causes clinically significant disease. In some cases, no therapeutic intervention is necessary and cosmetic camouflage may be sufficient. Indeed, treatment of HIV with antiretroviral therapy usually results in improvement, and in most cases, complete resolution, of Kaposi's sarcoma. When individual lesions are troublesome, local radiotherapy or intralesional vinblastine can be beneficial. Alitretinoin gel (0.1%) (9-*cis*-retinoic acid) is a topical, self-administered therapy approved for the treatment of KS in the USA but not licensed in Europe. In cases of widespread cutaneous disease or significant visceral involvement, systemic chemotherapy is used, though this is often withheld until the potential benefits of HAART have been established. The liposomal anthracyclines and taxanes are now the mainstay of systemic chemotherapy for Kaposi's sarcoma (Bower et al., 2008).

Lymphomas. The most common lymphomas in patients with HIV infection are high-grade B-cell (non-Hodgkin's) types. Primary central nervous system lymphomas, which are extremely rare in the general population, are more common in individuals with HIV infection but tend to occur only in those with severe immunosuppression. Diagnosis of lymphoma is usually based upon histological confirmation from biopsy specimens. This may not be possible for primary central nervous system disease. The advent of HAART has dramatically reduced the incidence of all lymphomas. However, whilst it has similarly improved the outcome for most cases, this is unfortunately not true for primary central nervous system lymphomas. Lymphoma of the central nervous system is associated with an extremely poor outcome, and in many cases, even palliative radiotherapy or corticosteroids confer little benefit.

The optimal therapy for HIV-associated lymphomas has yet to be determined, but the management plan should either be supervised by, or have input from, an oncologist with relevant specialist experience. The outcome for patients with relatively preserved immune function or those receiving HAART is comparable to that in the general population. However, many individuals are unable to tolerate treatment without dose modification. Drug interactions between antiretrovirals (particularly PIs) and chemotherapeutic agents need to be considered to minimise the risk of treatment-limiting toxicities, whilst the proactive use of colony-stimulating factors may enable optimal dosing.

Cervical intraepithelial neoplasia and anal intraepithelial neoplasia. These are both associated with human papillomavirus infection, are more common in individuals with HIV infection and may progress to cervical cancer and anal cancer, respectively. It is currently believed that HAART reduces the progression of cervical intraepithelial neoplasia (CIN) but this does not appear to be true of anal intraepithelial neoplasia (AIN), and there are concerns that the incidence of this malignancy may increase with improvements in HIV survival.

The optimal management is a combination of early diagnosis, surgery, chemotherapy and/or radiotherapy. It is possible that screening by smear tests and early treatment, for example, with imiquimod, may reduce the need for such aggressive treatment approaches.

Neurological manifestations

Neurological symptoms may be due to opportunistic infections, tumours or the primary neurological effects of HIV.

HIV encephalopathy or AIDS dementia complex (ADC) is believed to result from direct infection of the central nervous system with HIV itself. Individuals who may otherwise be physically well can be debilitated by profound cognitive dysfunction and amnesia. Although psychometric test results are

usually suggestive of the underlying aetiology, it is wise to rule out any other cause with brain scanning and CSF analysis.

The incidence of ADC has reduced dramatically with the use of HAART, and similarly, the use of HAART has been anecdotally associated with an improvement in outcome in many cases. Whilst it is known that the central nervous system penetration of some antiretroviral agents is better than others, the beneficial effects on ADC do not appear to be limited to those agents which penetrate well. Nonetheless, many clinicians would choose to include at least one agent with good penetration of the central nervous system in most HAART regimens, particularly in individuals with cognitive impairment. More recently, there have been increasing reports of more subtle cognitive impairment in patients with HIV receiving effective HAART therapy. The role of varying neuropenetrative agents in either the aetiology or the management of such patients is currently under investigation.

Progressive multifocal leucoencephalopathy (PML) is caused by JC virus and may, at presentation, appear similar to a cerebrovascular accident but will have characteristic white matter lesions on an MRI scan, with or without the presence of JC virus in the CSF. In many cases, the introduction of HAART prevents progression of disease, but it is unlikely to reverse the functional deficit at presentation. The role of adjunctive cidofovir in treatment remains controversial.

Hepatitis B co-infection

There are a number of ways in which HIV can impact on hepatitis B (HBV) infection:

- Hepatitis B vaccination is less successful
- Hepatitis B is less likely to be cleared and hence more likely to become chronic
- Hepatitis B infection is likely to be associated with higher hepatitis B DNA levels
- Progression to cirrhosis is more rapid
- Hepatocellular carcinoma is more common.

Although many individuals with HIV will have hepatitis B serological markers suggestive of previous infection, only 6–10% in most series have active hepatitis B infection.

Management requires an understanding of both viruses and is facilitated by the availability of drugs with dual HIV and hepatitis B activity (Brook et al., 2010). The HAART regimen should include two agents with anti-hepatitis B activity, usually tenofovir with either emtricitabine or lamivudine. If HIV develops resistance to these agents, they can still be continued for their anti-hepatitis B activity.

Hepatitis C co-infection

HIV also impacts on hepatitis C infection in a number of ways:

- Hepatitis C is less likely to be cleared spontaneously
- Higher levels of hepatitis C RNA are seen
- Hepatitis C progresses to cirrhosis more rapidly
- Hepatocellular carcinoma occurs more frequently
- Response to hepatitis C therapy is poor.

In the UK, approximately 5–10% of individuals are co-infected with hepatitis C; there are increasing reports of acute hepatitis C infection in gay men with HIV. In Eastern Europe, where the predominant route of HIV transmission is needle sharing, co-infection rates of over 50% are reported.

The management of hepatitis C/HIV co-infection is complicated (Brook et al., 2010). If treatment for hepatitis C is needed for someone on HAART, the antiretrovirals used must be compatible with hepatitis C therapy (pegylated α interferon and ribavirin). Didanosine, abacavir, stavudine and zidovudine should be avoided. It is commonplace to treat individuals with co-infection for a longer duration, for example, 48 weeks rather than 24 weeks for individuals with genotype 2 and 3 hepatitis C, and possibly 72 weeks for genotypes 1 and 4 – dependent upon early virological responses. Side effects of hepatitis C therapy tend to be more frequent and severe in the co-infected population. The proactive use of the colony-stimulating factors erythropoietin and G-CSF may enable optimal dosing of hepatitis C therapy and thereby improve outcome. The management of HCV is likely to be revolutionised by the availability of increasing numbers of Directly Acting Antivirals (DAAs) of which a large number are currently in development. The optimal way to use these and the potential drug-drug interactions with antiretrovirals have yet to be fully elucidated.

Women with HIV

In addition to the general points covered elsewhere in this chapter, specific issues for women with HIV include:

- Cervical screening should be carried out at least annually, to check for gynaecological manifestations of HIV
- Drug toxicity may manifest in different ways or occur with different frequencies, for example, nevirapine hypersensitivity reaction occurs at a lower CD4 count in women whilst lipodystrophy syndrome may also present differently, with breast hypertrophy commonly seen.

Pregnancy and contraception impact on the medicines prescribed for women of childbearing potential. The factors that need to be taken into account (where appropriate) may include:

- Interactions between many antiretrovirals and oral and injectable contraceptive agents (see Table 41.7). There are no interactions with the levonorgestrel-releasing intrauterine system, Mirena. (*Note*: barrier methods should also be recommended in addition to hormonal contraception, to prevent transmission of HIV and other sexually transmitted infections)
- Potential teratogenicity of the drugs prescribed
- Possible increased toxicity of the drugs prescribed to both mother and child
- The use of antiretroviral agents and other strategies to reduce vertical (mother-to-child) transmission of HIV.

The use of combination antiretroviral therapy, with or without caesarean section, with zidovudine as PEP to the neonate, together with a non-breast feeding strategy has reduced vertical transmission rates from 35% to less than 1% where HIV status is known and where antiretroviral therapies are widely available.

Table 41.7 Interactions between antiretroviral (ARVs) and contraceptive agents

	Combined oral contraceptive pill (COC)	Progesterone-only pill (POP)	Depot contraception-Depomedroxyprogesterone acetate (DMPA)	Implanon® Evra®
NNRTIs				
Efavirenz	C	C	A	C
Etravirine	A	A	B	B
Nevirapine	C	C	A	C
PIs				
Atazanavir/ritonavir	A Use COC with **at least** 30 µcg ethinyloestradiol. The increase in progestin exposure may lead to related side effects.	C	C	A
Atazanavir (unboosted)	A Use COC with **maximum** 30 µcg ethinyl estradiol	C	D	C
Darunavir/ritonavir	C	C	B	C
Foamprenavir/ritonavir	C	C	D	C
Indinavir (unboosted)	A	A	B	A
Lopinavir/ritonavir	C	C	B	C
Nelfinavir	C	C	A	C
Saquinavir/ritonavir	C	C	B	C
Tipranavir/ritonavir	C	C	B	C
Integrase inhibitors				
Raltegravir	A	A	A	A
CCR5 Antagonist				
Maraviroc	A	A	A	A
Entry inhibitors				
Enfuvirtide	A	A	A	A

A, combination can be used safely; B, no formal studies, but no clinically significant interactions expected; C, additional barrier contraceptive must be used or alternative method; D, avoid combination.

Nonetheless, questions remain regarding the optimal therapies to use, the risk of transmission of resistant virus to the neonate and the risk of toxicity from antiretroviral agents administered during pregnancy, particularly in the first trimester. Ideally, all HIV-positive women should be counselled regarding these issues before they become pregnant, so they can make informed decisions regarding both therapy and timing of pregnancy.

Guidelines are available that set out the management of HIV infection in pregnant women and the prevention of mother-to-child transmission (de Ruiter et al., 2008). In general, intervention reflects a risk/benefit evaluation between the efficacy of reducing transmission and the potential harmful effects to the mother and fetus. Where HAART is clinically indicated for the mother herself, this should utilise a regimen of optimal efficacy with a favourable safety profile. Where therapy is initiated to reduce transmission, this is usually a HAART regimen but could be zidovudine monotherapy if the viral load is low (consistently <10,000 copies/mL). In the latter situation, the time of therapy initiation is guided by the viral load (Read et al., 2010):

if <10,000 copies/mL – start by 26 weeks;
if >10,000 copies/mL – start by 20 weeks;
if >32,000 copies/mL – start without delay.

Adjunctive caesarean section is recommended where monotherapy is used or there is a detectable viral load prior to delivery, but may not be essential if the mother is on fully suppressive HAART. Breastfeeding should be avoided and antiretroviral therapy is usually administered to the newborn for 4 weeks after birth. In the developing world, different strategies may be adopted. For example, single-dose nevirap-

ine monotherapy is effective in reducing transmission but may be associated with the development of resistance, and exclusive breast feeding, with or without antiretrovirals for the baby, may be recommended where water safety is poor.

Ethnicity

It is now recognised that ethnicity as well as gender can affect drug handling and response to treatment. This is due, in part, to epidemiological differences in gene expression. For example, reduced activity of cytochrome P450 2B6, one of the key enzymes involved in the metabolism of NNRTIs, appears to be more common amongst Africans than Caucasians. These drugs, therefore, have a significantly longer plasma half-life in those affected, which may impact on efficacy, toxicity and treatment interruptions. The prevalence of the HLA*B5701 gene, associated with abacavir hypersensitivity, also varies in different ethnic groups, though the clinical implications of this have yet to be fully researched.

As pharmacogenomics becomes more widely incorporated into clinical trials and routine patient care, it is hoped that a greater understanding will be gained of differences in response to treatment, enabling treatment strategies to be individualised and optimised.

Case studies

Case 41.1

Ms A is a 21-year-old UK-born pharmacy student who presented to her primary care doctor with a rash, swollen glands and flu-like illness. A presumptive diagnosis of swine flu was made. She was given a course of oseltamavir (Tamiflu®) and her symptoms largely resolved over the following 2 weeks. Two months later, her male partner attended his dentist for a routine check up and was found to have oral candidiasis. He had no obvious predisposing factors and his dentist thus suggested that he have an HIV test, which was positive. As a result of this, Ms A was advised to have a test and was subsequently found to be HIV positive too, with a CD4 count of 420 cells/mm^3 and a plasma HIV RNA (viral load) of 610,000 copies/mL.

One year after her diagnosis, Ms A has had two consecutive CD4 counts below 350 cells/mm^3 (the latest being 310) and a viral load of 50,000–95,000 copies/mL. She is advised to start antiretroviral therapy and plans to do this in a few weeks as soon as she has finished her final exams. She currently takes no medication and uses condoms for contraception/sexually transmitted infection prevention. You are part of the multidisciplinary team which will recommend the regimen to be offered/prescribed.

Questions

1. What is the most likely diagnosis for the illness Ms A initially presented with to her primary care doctor?
2. What baseline investigation results would you need to inform your choice of antiretroviral therapy?
3. What would you do if there was a need to start therapy urgently and these results were not available?
4. Assuming all results were normal, which antiretroviral therapy regimen would you suggest and why?
5. What are the main counselling points to discuss with Ms A when she starts antiretroviral therapy?

Answers

1. The most likely diagnosis is PHI, also known as seroconversion syndrome. Approximately 70% of people newly infected with HIV develop PHI symptoms, typically a flu-like illness, with fever, arthralgia, pharyngitis, rash and lymphadenopathy.
2. The most important HIV-specific investigation which must be performed prior to starting treatment is an HIV resistance test (usually a genotype). Failure to do this can result in premature treatment failure and rapid development of multiple class drug resistance. The presence of HIV resistance mutations is likely to affect the choice of regimen.

   Some clinicians would also perform tropism testing at this point, that is, immediately prior to starting therapy, but it would be unlikely to affect treatment choice at this stage, and hence antiretroviral therapy can be started before the result is available, which may be 6 weeks. The rationale for carrying out a tropism test now, even though a CCR5 inhibitor is not generally used first line, is that antiretroviral agents may subsequently need to be changed when the viral load is undetectable, due to toxicity or intolerance. In addition, the Trofile® test can only be reliably performed on samples with a viral load >1000 copies/mL. However, different tropism tests, which can be carried out on samples with low/undetectable viral load, are now available.

   HLA B*5701 testing might also be done at this stage. If negative, there is an extremely low probability of developing a hypersensitivity reaction on exposure to abacavir, should this drug be considered either at this stage or if treatment needs to be switched in future.

   Routine baseline blood tests (U&Es, eGFR, LFTs, etc.) should also be done to assist antiretroviral therapy choice and monitor for subsequent adverse effects. Some clinicians would also perform a urine protein creatinine ratio (UPCR) before starting a tenofovir-containing regimen.

   While CD4 count is a useful indicator of when to start treatment, and both CD4 and viral load are invaluable in monitoring antiretroviral therapy success, they do not usually influence the choice of agents.
3. Genotypic resistance test results usually take about 3 weeks to be reported, so if therapy needs to be started sooner (as in someone newly diagnosed with a CD4 count <200 cells/mm^3), then a regimen must be selected that has at least one drug with a high genetic barrier to resistance and to which primary resistance is unlikely to be present. In this case, a ritonavir-boosted PI, such as darunavir 800 mg daily or atazanavir 300 mg daily, with ritonavir 100 mg daily, would usually be combined with two nucleoside/nucleotide reverse transcriptase inhibitors (e.g. Truvada® or Kivexa® 1 tablet daily). Non-nucleosides (NNRTIs) and integrase inhibitors should be avoided in this situation because they have a low genetic barrier to resistance, that is, the presence of a single resistance mutation is sufficient to render them ineffective.
4. If there was no baseline resistance and other blood results were within normal limits, a typical initial regimen would be two NRTIs and an NNRTI, such as Kivexa® (abacavir and lamivudine) and efavirenz or tenofovir, emtricitabine and efavirenz. The latter is available as a combination tablet (Atripla®, 1 tablet daily) which is widely prescribed as a first antiretroviral therapy combination. Although the UK licensed indication is currently only for adults whose viral load has been maintained at <50 copies/mL for >3 months on antiretroviral therapy (e.g. on the same drugs, but

taken as Truvada®, or tenofovir and emtricitabine, plus efavirenz), it is common practice to initiate therapy with Atripla.

5. Medication counselling should include:
   - What the medication is and how to take it, as well as any specific storage conditions (eg tenofovir-containing preparations contain a desiccant)
   - Potential side effects and how to prevent them, what to do and who to contact about them including out of hours. Check the Summary of Product Characteristics (www.medicines.org.uk) for the specific side effects of the drugs chosen. Generally, patients should be counselled on common/very common or serious potential effects which they may notice or those which will be monitored
   - Relevant drug interactions, including with prescribed medicines, herbal and over-the-counter (OTC) preparations, recreational drugs and alcohol
   - What to do if a dose is missed, administered late or the patient vomits soon after taking a dose
   - The rationale for, and importance of, a high level of adherence for successful treatment, outlining services that are available to support her, such as provision of adherence aids.

Case 41.2

In 1995, Mr B, a 47-year-old man, presented with *P. jiroveci* pneumonia. He had a CD4 count of 123 cells/mm^3, and plasma HIV RNA was unknown, as viral load testing was not routinely available in clinics at the time. He made a good response to treatment with high-dose co-trimoxazole and was subsequently commenced on dual combination therapy with zidovudine and zalcitabine (ddC, an NRTI, no longer marketed). He remained on this regimen for 18 months, until HIV RNA testing became available and he was found to have a viral load of 13,000 copies/mL and CD4 242 cells/mm^3. His full antiretroviral therapy history, with reasons for switching, is detailed as follows (Table 41.8).

In September 2009 (now aged 62), his viral load remained <40 copies/mL, with CD4 670 cells/mm^3. However, his creatinine clearance (calculated using Cockcroft-Gault equation) was 41 mL/min and urine protein:creatinine ratio was significantly raised, at 86 mg/mmol (normal <30 mg/mmol). Both were normal when last monitored 4 months previously. On questioning, he revealed that he had been taking regular ibuprofen (400 mg three times a day) for the past month, following a wrist fracture, as well as bendroflumethiazide 2.5 mg daily and tamsulosin 400 µcg daily, both of which he has been taking for more than 2 years.

Question

1. What are the possible drug-related causes of his renal dysfunction and what alterations, if any, to his drug therapy would you recommend?

   Two weeks after stopping the ibuprofen, Mr B's creatinine clearance is now 52 mL/min and he is prescribed Atripla® 1 tablet daily. His repeat urine protein:creatinine ratio, 1 week after stopping ibuprofen was 42 mg/mmol (improving), with normal urine albumin:creatinine ratio. His serum phosphate was low and fractional excretion of phosphate was 35% (normal < 25%). Although his renal function was improving, it was decided to recommend changing his antiretroviral therapy to boosted darunavir (PI monotherapy), darunavir 800 mg daily and ritonavir 100 mg daily.
2. What information should Mr B be given about the proposed change of regimen?

Answer

1. Tenofovir use has been associated with renal dysfunction, the first sign of which may be a raised UPCR, although there are other causes. Mr B has a raised UPCR and reduced creatinine clearance, suggesting moderate renal dysfunction, which may be tenofovir related. However, regular concomitant NSAIDs and bendroflumethiazide may increase the risk of renal dysfunction. It is possible that the addition of regular ibuprofen has precipitated the renal dysfunction. Therefore, he would be advised to change to an alternative analgesic, if one is still required, starting with regular paracetamol.

   Atripla is not recommended for patients with creatinine clearance <50 mL/min, as the doses of emtricitabine and tenofovir need to be adjusted. For creatinine clearance 30–49 mL/min, a dose of 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (245 mg tenofovir disoproxil) every 48 h is required. The efavirenz dose remains 600 mg daily. However, Mr B's renal function must be closely monitored, for example, twice a week, to ensure that the doses are adjusted promptly to reflect any

Table 41.8 Mr B's ARV treatment history (Case 41.2)

Start date	Drug name, dose and frequency	Stop date	Viral load and CD4 at switch	Reason for changing
Nov 1995	Zidovudine 200 mg tds Zalcitabine 750 µgrams tds	May 1997	VL 13000 CD4 242	Virological failure
May 1997	Stavudine 40 mg bd Didanosine 200 mg bd Indinavir 800 mg tds	Apr 1999	VL <200 (lower limit of detection at that time) CD4 412	Renal stones (indinavir)
Apr 1999	Stavudine 40 mg bd Didanosine 200 mg bd Efavirenz 600 mg od	Jan 2002	VL <50 (lower limit of detection at that time) CD4 503 (stavudine and didanosine)	Lactic acidosis
Jan 2002	Tenofovir df 300 mg od Lamivudine 300 mg od Efavirenz 600 mg od	Mar 2008	VL <40 CD4 633	Simplification (Reduction in number of tablets)
Mar 2008	Atripla 1 tablet od			

change. This is to avoid over- or underdosing, and the associated risks of toxicity and antiretroviral therapy failure.

If the renal dysfunction continued or worsened, despite stopping the ibuprofen and dose adjusting his antiretroviral therapy, the choice of diuretic could be reviewed. If the problem still persists, then a change of antiretroviral therapy might be warranted.

2. Although the use of ritonavir-boosted darunavir monotherapy (darunavir/ritonavir) is an unlicensed indication, there are data from clinical trials, for example, Arribas et al. (2010), to support this approach. Mr B should be informed of this. Other discussion points should include:
   - How to take the new regimen: two darunavir 400 mg tablets, plus one ritonavir 100 mg tablet, taken together once daily, at the same time each day (±1 h), with or after food
   - How to switch from Atripla® to the new regimen. Atripla® is taken on an empty stomach, usually at night, to reduce CNS side effects and he may wish to take his new antiretroviral therapy at a different time. If he does this, he should ensure the interval between the last dose of Atripla® and the first dose of darunavir/ritonavir is no longer than 25 h
   - Storage conditions: Atripla® is supplied with a desiccant; darunavir and ritonavir tablets do not have any special storage requirements.

Case 41.3

Mr C is a 58-year-old homosexual man who was diagnosed HIV positive 25 years previously but has never had any AIDS-defining illnesses. He received 16 months of zidovudine monotherapy during 1993–1994 as part of a study but subsequently remained off therapy until 1996 when, following a fall in his CD4 count to 240 cells/mm^3, he was commenced on stavudine, lamivudine and indinavir. His response was excellent, with a rise in his CD4 count to 520 cells/mm^3 and a viral load below detection (<50 copies/mL), but in 1999, the indinavir was changed to Kaletra®, following an admission to hospital with indinavir-induced nephrolithiasis. In 2003, when his viral load was still undetectable, the stavudine was switched to abacavir because of marked facial and peripheral lipoatrophy. The facial wasting was successfully treated with a course of polylactic acid (New-Fill®) injections, and there has been a small, gradual natural recovery of subcutaneous limb fat. He has been on pravastatin 40 mg once daily and fenofibrate 160 mg once daily since 2000, when he also stopped smoking.

At his annual health review, his most recent surrogate markers remained excellent, with a CD4 count of 1100 cells/mm^3 and a viral load of <40 copies/mL. However, his fasting lipids were total cholesterol 5.9 mmol/L, LDL cholesterol 4.5 mmol/L, HDL 1.0 mmol/L, triglycerides 3.3 mmol/L. His calculated creatinine clearance (Cockcroft and Gault equation) was 45 mL/min (it was >50 mL/min when last checked 4 months ago), he had a fasting glucose of 9 mmol/L and had a raised blood pressure (BP 140/95 mmHg confirmed on two separate occasions). His 10-year cardiovascular risk was calculated to be 21.5%.

Questions

1. What are the limitations of using this cardiovascular risk calculator in this situation? Is the calculated risk likely to be an over- or under-estimate and why?
2. Mr C is concerned about the implications of his annual health review results. What information and advice should he be given?
3. What changes to his drug therapy might you recommend?

Answers

1. The main limitation of using any cardiovascular risk calculator is that the population data underpinning it come from individuals whose HIV status was not recorded. HIV infection itself is thought likely to increase the risk of cardiovascular disease, but there is currently insufficient evidence of the extent of additional risk to be able to quantify this in any of the established cardiovascular disease risk calculations. In addition, some antiretrovirals, for example, abacavir, didanosine and Kaletra have been shown to be associated with an increased risk of cardiovascular disease. This is also not factored into any of the existing cardiovascular risk calculators. In addition, Mr C is already on lipid-lowering therapy, so his untreated lipid markers would be expected to be more abnormal. The calculated 10-year risk of 21.5% is therefore likely to be an underestimate.
2. Mr C should be given general lifestyle advice to follow a healthy balanced diet and take aerobic exercise at least three times a week. Specific lipid-lowering dietary advice could be given. It would be useful to establish if Mr C has changed his lifestyle in the last 4–6 months, for example, change in adherence to lipid-lowering therapy, change in diet, restarted smoking, taking any new medication, including non-prescription and herbal medicines. Any relevant cardiovascular risk factors should then be discussed/addressed. The possibility that two of his antiretrovirals may also be contributing to his cardiovascular risk should also be explained.
3. Given Mr C's high cardiovascular risk, a change of antiretroviral therapy should be considered. The risk associated with Kaletra® use appears to be cumulative, that is, related to length of time on treatment, whereas the data on the nature of the risk associated with abacavir are less clear. However, it would be appropriate to explore the options for changing his antiretroviral therapy. Currently, there are no data on the presence or absence of cardiovascular risk associated with the other two commonly used boosted PIs, atazanavir and darunavir. In the absence of any HIV resistance test results dating from soon after he stopped the zidovudine monotherapy, it should be presumed that some NRTI mutations may be 'archived'. Caution should therefore be exercised before prescribing combinations with a low genetic barrier to resistance, for example, those containing NNRTIs or integrase inhibitors, without PIs.

   Assuming Mr C's adherence to his lipid-lowering agents had been good, a change of therapy could be indicated, for example, pravastatin to atorvastatin. It would be reasonable to start with 20 mg atorvastatin, increasing to 40 mg if necessary and tolerated. However, if his antiretroviral therapy is going to be changed, it may be helpful to plan the changes in a stepwise fashion, so that the impact of each adjustment can be assessed. In this case, the lipid-lowering therapy alterations should be effected after the change of antiretroviral therapy. A change to simvastatin would be contraindicated if he remains on a PI.

Case 41.4

Ms D is a 50-year-old social worker who was referred to the hospital accident and emergency department by her primary care doctor following a 4-week history of worsening respiratory symptoms, despite treatment with amoxicillin, followed by clarithromycin. She has lost 3 kg in the last 2 months, has had a non-productive cough for 6 weeks and gets breathless climbing the stairs at home. Pulse oximetry showed desaturation to 91% on exercise and her arterial blood gas sample had a PaO_2 of 8.1 kPa. Chest X-ray showed bilateral interstitial infiltrates. Her past medical history includes irritable bowel syndrome (diagnosed

5 years ago), recurrent vaginal candidiasis for the past 7 years and allergic rhinitis for which she uses fluticasone nasal spray. She is divorced and has a 10-year-old son. She works in an inner city area and has no history of foreign travel outside mainland Europe. The hospital has recently introduced routine (opt out) HIV testing for all acute medical admissions, as a result of which Ms D was found to be HIV positive, with a CD4 count of 47 cells/mm^3.

Questions

1. What are the most likely HIV-related differential diagnoses for her respiratory symptoms?
2. How should her respiratory symptoms be managed?
3. When should she start antiretroviral therapy?
4. What drug interactions would you need to consider when managing Ms D both in the first few weeks and also in the longer term?

Answers

1. The history, signs and symptoms (gradual onset, failure to respond to treatment for community acquired pneumonia, weight loss, non-productive cough, breathlessness on exertion, oxygen desaturation, low PaO_2 and chest X-ray appearance) are all suggestive of *P. jiroveci* pneumonia. However, some of them could also be consistent with TB which she may have been exposed to as a result of the nature and location of her job. TB would need to be excluded. As Ms D has a significant degree of immunesuppression, the possibility of more than one pathogen/diagnosis must always be considered.
2. Until TB has been excluded, Ms D should be nursed in a negative pressure room. A bronchoscopy should ideally be performed to assist diagnosis. She should be started on treatment for *P. jiroveci* pneumonia immediately with high-dose co-trimoxazole and systemic corticosteroid (see text and Table 41.8 for doses and administration details). Following induction treatment (usually 3 weeks' duration), she should receive secondary prophylaxis until her CD4 count on fully suppressive antiretroviral therapy is maintained above 200 cells/mm^3.

   If she responds well to *P. jiroveci* pneumonia treatment and bronchial washings are negative for acid-fast bacilli, then it would be reasonable for her to be managed expectantly with regard to the possibility of TB, that is, not kept in isolation and not started on TB treatment unless relevant symptoms persist or worsen, or new ones develop.

   If TB treatment were required, the standard four-drug (rifampicin, isoniazid, pyrazinamide, ethambutol) 2-month induction regimen, followed by 4 months of rifampicin and isoniazid, plus pyridoxine would be recommended.
3. With a CD4 count of 47 cells/mm^3, treatment with antiretroviral therapy would be recommended as soon as possible. Depending on how well she tolerated and responded to the *P. jiroveci* pneumonia treatment, and whether or not TB treatment was also needed, antiretroviral therapy would usually be started within 2–4 weeks of diagnosis. For more information, refer to British HIV Association guidelines for management of opportunistic infections (Nelson et al., 2010) and TB/HIV co-infection (Pozniak et al., 2010).
4. If Ms D did require TB treatment, the hepatic enzyme induction effect of rifampicin would need to be considered. For example, the dose of co-trimoxazole for *P. jiroveci* pneumonia prophylaxis should be a minimum of 960 mg once daily when co-administered with rifampicin.

   The choice and dose of antiretroviral therapy would also be affected if treatment was started after the HIV genotypic resistance test result was known; if no resistance had been found, then efavirenz-containing antiretroviral therapy would be possible. If co-administered with rifampicin, the efavirenz dose should be increased to 800 mg once daily. This would ideally be followed by TDM 2 weeks later, with further dose adjustment if necessary. Although the utility of antiretroviral therapy TDM remains controversial, this is a situation where it is commonly used.

   If PI-based antiretroviral therapy were initiated, either because of the presence of resistance mutations or whilst awaiting the HIV resistance test result, then TB therapy (if required) would need to be altered. Rifabutin (150–300 mg three times a week) would be used instead of rifampicin. PIs also interact with intranasal and inhaled fluticasone and budesonide, resulting in systemic absorption of these steroids, due to inhibition of cytochrome 450 3 A4 in the gut wall and the liver. Beclometasone nasal spray would be a suitable alternative preparation for Ms D's allergic rhinitis.

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Useful websites

British Association for Sexual Health and HIV:
www.bashh.org
British HIV Association:
www.bhiva.org
Clinical Care Options (US-based website focusing on HIV, hepatitis and oncology):
www.clinicaloptions.com
European AIDS Clinical Society Guidelines:
www.europeanaidsclinicalsociety.org/guidelines.asp
HIV i-Base (UK-based community provider of wide range of HIV-related information, including drug/treatment updates, conference reports and daily news items):
i-base.info/home/

Johns Hopkins University HIV Guide:
www.hopkins-aids.edu
Medscape (US-based medical website with HIV specialty home page):
www.medscape.com
NAM (UK-based community provider of wide range of HIV-related information, including drug/treatment updates, conference reports and daily news items):
www.aidsmap.com
Toronto General Hospital Immunodeficiency Clinic:
www.hivclinic.ca/main/home.html
United States National HIV Guidelines (antiretroviral treatment, management of opportunistic infections, co-infections and post-exposure prophylaxis):
www.aidsinfo.nih.gov/guidelines/
University of California San Francisco HIV Educational Resource:
www.hivinsite.ucsf.edu
University of Liverpool HIV Pharmacology Group (includes drug interaction charts):
www.hiv-druginteractions.org

42 Fungal infections

M. Narayanan

Key points

- Fluconazole, a triazole, is considered to be standard therapy for oropharyngeal, oesophageal and vaginal candidiasis.
- Itraconazole and terbinafine are efficacious, non-toxic alternatives to griseofulvin when systemic treatment of dermatophytosis is required.
- Fungi can cause overwhelming deep-seated or systemic infections in immunocompromised hosts that are refractory to antifungal treatment alone.
- Incidence of non-Aspergillus mould infections has increased in transplant recipients over the past decade, and these can be lethal.
- Most therapy for deep-seated fungal infection in the immunocompromised host is empirical due to the difficulties in reaching a rapid, accurate diagnosis of systemic fungal infection.
- Lipid-complexed formulations of amphotericin offer a less toxic alternative to conventional amphotericin in the treatment of systemic fungal infection.
- Voriconazole, a triazole, appears to be an effective alternative to amphotericin in the treatment of invasive aspergillosis.
- Caspofungin is an alternative agent to amphotericin for invasive aspergillosis and may have a role to play in the empirical treatment of febrile neutropenic patients.

Fungi are ubiquitous microorganisms that differ from bacteria in their cellular structure, and this makes them naturally resistant to antibacterial agents (Table 42.1). Fungi are broadly divided into yeasts and moulds. Yeasts are typically round or oval shaped microscopically, grow flat round colonies on culture plates and reproduce by forming buds from their cells. Moulds (e.g. *Aspergillus*, *Mucor*) appear as a collection or mass (mycelium) of individual tubular structures called hyphae that grow by branching and longitudinal extension. They appear as a fuzzy growth on appropriate conducive medium (e.g. *Penicillium* colonies on stale bread or Sabourauds agar). The most commonly seen yeast, *Candida*, occasionally produces pseudohyphae.

There are hundreds of species of fungi found in the environment, but only the important human fungal pathogens and their treatment will be discussed in this chapter. The fungi of medical importance can be divided into four groups (Table 42.2).

Some fungi like *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis* are known as dimorphic fungi (Table 42.2) because they are found in the infected host in yeast form at 35–37 °C temperature but grow as moulds, *in vitro*, at room temperatures (22 °C incubation).

Fungi mainly reproduce by forming spores through mitosis giving rise to two daughter cells. They are known by names given to this imperfect state (asexual reproduction), but the same fungus, for example, *Scedosporium apiospermum* (asexual form) is also known as *Pseudoallescheria boydii* (sexual form). However, for all practical purposes, only the oldest and best-established name for the fungi is used in diagnostic laboratories.

Fungal spore are spread by air, water and direct contact with infected source. Humans usually become infected by inhalation of airborne spores or by inoculation into traumatised skin and mucous membrane.

Laboratory diagnosis

Microscopical examination and culture of fungi is the mainstay of laboratory diagnosis. Appropriate staining of histological sections of affected tissue is helpful in making a

Table 42.1 Important characteristics of a fungal cell

Fungi	Bacteria
Eukaryotes	Prokaryotes, eubacteria
Cell and cytoplasm	Cell and cytoplasm
Nucleus with multiple chromosomes enclosed in a nuclear membrane	No nucleus or nuclear membrane, has single chromosome
Contains endoplasmic reticulum, golgi apparatus, mitochondria and ribosomes	Other structures absent except ribosomes
Cytoplasmic membrane	Cytoplasmic membrane
Contains phospholipids and sterols	Contains phospholipids and no sterols
Cell wall	Cell wall
Contains chitins, mannans,+/- cellulose	Contains peptidoglycan, lipids and proteins

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Table 42.2 Classification of fungi of medical importance

Group	Examples	Infections caused
Yeast	*Candida* spp.	Oral and vaginal thrush Deep seated: candidaemia, empyema
	Cryptococcus neoformans	Meningitis
	Saccharomyces cervesiae	Rare systemic infection in immunocompromised host
	Malassezia furfur	
Yeast-like	*Geotrichium candidium*	
	Trichosporon beigelii	
Dimorphic fungi	*Blastomyces dermatitidis*	For first three: deep systemic organ involvement, more commonly in the immunocompromised host
	Coccidioides immitis	Deep subcutaneous infection following trauma
	Histoplasma capsulatum	
	Paracoccidioides brasiliensis	
	Sporothrix schenckii	
Moulds 1. Hyaline		
a. Zygomyces	*Rhizopus*	Infections in neutropenic patients and those with diabetic ketoacidosis
	Mucor	
	Absidia	
b. Hyalohyphomycosis	*Aspergillus fumigatus* and other	Systemic infection: invasive pulmonary or central nervous system involvement
	Aspergillus spp.	
	Fusarium	Fusarium keratitis
	Scedosporium apiospermum	Deep infection in immunocompromised host, for example, transplant patients
2. Dermatophytes	*Trichophyton* spp. *Microsporum* spp. *Epidermophyton*	For all three: various skin (ringworm) hair and nail infections
3. Dematiaceous	*Alternaria* spp.	Deep tissue infection with granulomas
	Cladophialora spp.	Chromomycosis, mycetomas

diagnosis when culture growth may or may not be positive. Yeast colonies and moulds are characteristic in their appearance on culture plates and can be preliminarily identified by their shape, colour and temperatures at which they grow. For the genus and species identification of yeasts, microscopic examination and biochemical tests are necessary. Moulds are identified by their morphology and the nature of sporulation on agar medium.

Antifungal sensitivity testing for yeast is done by determining the minimum inhibitory concentration (MIC) of the antifungal agent in the E test® strip method which has now replaced the measurement of 'inhibition zone' by disc testing. E-test® strips are also available for determining sensitivity of antifungal agents against moulds. Molecular diagnosis utilising polymerase chain reaction (PCR) is not available for use in routine practice. Serological diagnosis to look for antibodies in patient's blood is of use only in *Coccidioides* infection. Enzyme-linked immunosorbent assay (ELISA) methods to look for galactomannan antigen in deep *Aspergillus* infection are available but not fully evaluated. A positive test needs to be interpreted in conjunction with other findings. Antigen detection is useful in disseminated *Histoplasmosis* and *Cryptococcosis*.

Fungal infection

It is important to distinguish harmless colonisation with fungi and significant infection, as only the latter would benefit from antifungal treatment.

More often, fungi are a cause of superficial infections of the skin and mucous membranes.

In some susceptible hosts whose immune system is heavily compromised, deep-seated infections involving organs like lungs and brain can manifest as 'difficult to cure' infections, for example, pulmonary aspergillosis or cryptococcal meningitis.

Antifungal agents

Topical and systemic antifungal agents are available to treat mucocutaneous candidiasis, various forms of tinea (ringworm) and other dermatophytosis, onychomycosis and deep-seated systemic infections (e.g. candidaemia, mucor mycoses, fungal endocarditis, osteomyelitis). Some infective conditions and their treatment are dealt with in the sections that follow. The side effects of a range of antifungal agents are set out in Table 42.3.

Table 42.3 Side effects of antifungal agents

Drug	Side effects
Griseofulvin	Mild: headache, gastro-intestinal side effects. Hypersensitivity reactions such as skin rashes, including photosensitivity Moderate: exacerbation of acute intermittent porphyria; rarely, precipitation of systemic lupus erythematosus. Contraindicated in both acute porphyria, systemic lupus erythematosus, pregnancy and severe liver disease
Terbinafine	Usually mild: nausea, abdominal pain; allergic skin reactions; loss and disturbance of sense of taste. Not recommended in patients with liver disease
Amphotericin	Immediate reactions (during infusion) include headache, pyrexia, rigors, nausea, vomiting, hypotension; occasionally, there can be severe thrombophlebitis after the infusion Nephrotoxicity and hypokalaemia Anaemia due to reduced erythropoiesis Peripheral neuropathy (rare) Cardiac failure (exacerbated by hypokalaemia due to nephrotoxicity) Immunomodulation (the drug can both enhance and inhibit some immunological functions)
Flucytosine	Mild: gastro-intestinal side effects (nausea, vomiting). Occasional skin rashes Moderate: myelosuppression (dose related), hepatotoxicity
Fluconazole	Mild: nausea, vomiting and occasional skin rashes; occasionally, elevated liver enzymes (reversible) Moderate or severe: rarely, hepatotoxicity and severe cutaneous reactions, especially in AIDS patients
Itraconazole	Mild: nausea and abdominal pain; occasional skin rashes Moderate or severe: rarely, hepatotoxicity
Voriconazole	Similar to fluconazole and itraconazole Mild: reversible visual disturbances occur in about 30% patients
Caspofungin	Mild: gastro-intestinal side effects; occasional skin rashes

Superficial infection

Candida infections

Epidemiology

Candida is a normal commensal of the human gastro-intestinal tract and skin. Loss of skin and mucosal integrity or use of broad-spectrum antibiotics which alter normal bacterial flora allow overgrowth of endogenous *Candida*. There are more than 100 species of *Candida*, but only a few are important as common human pathogens.

Thrush is candidal infection of the mucous membrane. It can manifest as oral infection, for example, oral thrush in various patient groups, vulvo vaginal thrush in females, balanitis in the uncircumcised man or intertrigo infection in moist skin surfaces in close proximity, for example, groin area. Patients with diabetes and steroid users, whether inhaled or oral, are also prone to infections. Dysphagia due to candidal oesophagitis presents in patients with AIDS and cancer.

Clinical presentation

Oral thrush typically presents as a sore mouth with white curd like patches on the tongue or oral mucosa which can bleed on scraping. Females with vaginal thrush present with itching and a creamy vaginal discharge. Skin infection in babies can present as pustular body rash or nappy rash in the moist perianal area. Candida folliculitis may present in unkempt, bearded men. Nail infection with *Candida* (onychomycosis), or subcutaneous tissue involvement under the nail (paronychia) is seen in people whose occupation involves prolonged hand immersion in water.

In severe oesophageal candidiasis, ulceration or formation of pseudomembranes and, rarely, perforation of lower third of the oesophagus may occur.

Candida can be a cause of hospital-acquired infection in patients as it is found in the hospital environment on inanimate objects or on skin of health care workers.

Treatment

Oral and vaginal candidiasis may be treated by either topical or systemic antifungal agents. The drugs currently available for topical use fall into two groups: the polyenes, of which only amphotericin and nystatin are used clinically, and the imidazoles such as econazole, clotrimazole, miconazole and fenticonazole. These agents are essentially identical in their antifungal activity and the only reasons to choose between them are price and differing preparations. The two systemic agents are both triazoles (fluconazole and itraconazole) and can be given by mouth. Skin infections may also be treated topically, but nail infections are unlikely to respond to a

topical antifungal agent alone and require systemic treatment. Oesophagitis will invariably require systemic treatment.

Topical treatment. The polyenes are broad-spectrum antifungal agents that are virtually insoluble in water and which are not absorbed from the gastro-intestinal tract or from skin or mucous membranes. Both nystatin and amphotericin (but particularly nystatin) are available in a wide range of formulations including pessaries, creams, gels, tablets, pastilles, etc. The choice of formulation clearly depends on the site of infection and patient preference.

Systemic treatment. Three triazole agents: fluconazole, itraconazole and voriconazole are available for systemic treatment of oral and vulvo vaginal candidiasis (VVC). A good source of advice on treatment is that from the Infectious Diseases Society of America (Pappas et al., 2009):

Vulvo vaginal candidiasis

- Several topical antifungal agents provide effective therapy; no agent is clearly superior
- A single 150-mg dose of fluconazole is recommended for the treatment of uncomplicated cases
- For recurring vulvo vaginal candidiasis, 10–14 days of induction therapy with a topical or oral azole, followed by fluconazole at a dosage of 150 mg once per week for 6 months, is recommended
- Complicated vulvo vaginal candidiasis requires topical therapy for 7 days or multiple doses of fluconazole (150 mg every 72 h for 3 doses). Recurrent infections with non-albicans *Candida*, for example, *C. glabrata,* may be more difficult to treat.

Candida balanitis

- Candida balanitis can be treated with topical polyenes or imidazoles, or with systemic fluconazole in the same dose as for vaginal infection.

It is sometimes stated that when treating a woman with vaginal candidiasis, the male partner should be treated simultaneously to prevent reinfection. Although there is no evidence to support this approach, it may be considered in women who suffer from repeated vaginal candidiasis.

Guidance on the treatment of topical and systemic therapy (Pappas et al., 2009) are also available for treatment of mild, moderate and severe oropharyngeal and oesophageal candidiasis and suppressive therapy for patients with HIV infection.

Dermatophytosis

Epidemiology

Dermatophytosis, or tinea, is a condition caused by three genera of dermatophyte fungi: *Trichophyton*, *Epidermophyton* and *Microsporum.* Unlike *Candida*, these are moulds which have a predilection for keratinised tissue such as skin, nail and hair. These fungi are very widely distributed throughout the world and may be acquired from the soil (anthrophilic, e.g. *Trichophyton rubrum*), from animals (zoophilic) or from humans (geophilic) infected with the fungus.

Some species are prevalent throughout the world, for example, *Microsporum canis,* while some are area specific, for example, *Trichophyton mentagrophyte* in Europe and New Zealand.

Clinical presentation

The classical clinical presentation of dermatophyte infection of the skin is ringworm (tinea), a circular, inflamed lesion with a raised edge and associated skin scaling. However, presentation is influenced by the site of infection, for example, tinea pedis (athlete's foot) between the toes, tinea cruris on the body, and by the actual species of fungus causing the infection. In general, less severe lesions are produced by human fungal strains, while those acquired from animals can produce quite intense inflammatory reactions.

Dermatophytosis of the nail results in thickened, discoloured nails, while in the scalp, infection presents with itching, skin scaling and inflammation, and patchy hair loss (alopecia).

Rarely, deep dermatophytosis may be seen in immunocompromised patients with involvement of subcutaneous tissue (granuloma).

Diagnosis

The diagnosis of dermatophyte infection is confirmed by collecting appropriate specimens such as material from infected nails and skin. The fungi can be seen microscopically and specimens may also be cultured, but antifungal susceptibility testing is not required.

Treatment

Small or medium areas of skin infection can be treated with topical therapy, but nail, hair and widespread skin infection should be systemically treated with oral antifungal agents.

The most commonly used topical agents are the imidazoles, of which a wide variety is available, including clotrimazole, ecoazole, miconazole, sulconazole and tioconazole. There is little to choose between these agents, all of which are usually applied two or three times daily, continuing for up to 2 weeks after the lesions have healed. Side effects are uncommon and usually consist of mild skin irritation. Other topical agents include amorolfine, terbinafine and tolnaftate.

The main oral antifungals used for dermatophytosis are terbinafine, itraconazole and fluconazole. Griseofulvin is an alternative treatment for tinea capitis.

Terbinafine. Terbinafine was the first member of a new class of antifungal agents, the allylamines, which became available for systemic use. These agents act by inhibition of the fungal enzyme squalene epoxidase, an enzyme involved in the synthesis of ergosterol, an essential component of the fungal cytoplasmic membrane. Although terbinafine has a very broad antifungal spectrum in the laboratory, its *in vivo* efficacy does not correspond to its *in vitro* activity, and it is used only for the treatment of dermatophyte infection.

Terbinafine is the treatment of choice for tinea infections at 250 mg/day for 2–4 weeks, 250 mg/day for 6 weeks for fingernail infection and 12 weeks for toenail infection.

About 70% of an oral dose of terbinafine is absorbed, and the drug appears in high concentrations in the skin. The half-life is about 16–17 h, and therefore the drug can be given once per day. Terbinafine is metabolised in the liver and the metabolites are excreted in the urine so that hepatic or renal dysfunction will prolong the elimination half-life.

Table 42.4 Conditions predisposing to systemic or deep-seated fungal infection

Infection	Predisposing conditions
Systemic candidiasis	Neutropenia from any cause (disease or treatment) Use of broad-spectrum antibiotics which eliminate the normal body flora Indwelling intravenous cannulae, especially when used for total parenteral nutrition Haematological malignancy and HSCT Solid organ transplantation AIDS (particularly associated with severe mucocutaneous infection) Intravenous drug abuse Cardiac surgery and heart valve replacement, leading to *Candida* endocarditis Gastro-intestinal tract surgery Oesophagectomy leak leading to pleural space infection (empyema)
Aspergillosis	Neutropenia from any cause, especially if severe and prolonged Acute leukaemia Solid organ transplantation (mainly lungs) Chronic granulomatous disease of childhood (defect in neutrophil function) Pre-existing lung disease (usually leads to aspergillomas; fungus balls form in the lung rather than invasive or disseminated infection)
Cryptococcosis	AIDS Systemic therapy with corticosteroids Renal transplantation Hodgkin's disease and other lymphomas Sarcoidosis Collagen vascular diseases
Zygomycosis	Diabetic hyperglycaemic ketoacidosis (leading to rhinocerebral infection) Severe, prolonged neutropenia Burns (leading to cutaneous infection)

HSCT, hematopoietic stem cell transplantation.

Itraconazole is the second preferred agent at 200 mg/day for 1–2 weeks and longer, with repeated courses for finger and toenail involvement.

Griseofulvin. The first orally administered treatment for dermatophytosis was griseofulvin, which has now been available for over 40 years. Griseofulvin is active only against dermatophyte fungi and is inactive against all other fungi and bacteria. In order to exert its antifungal effect, it must be incorporated into keratinous tissue, where levels are much greater than serum levels, and therefore it has no effect if used topically.

The usual adult dose is 10–20 mg/kg/day for 6 weeks for treatment of larger lesions in tinea corporis.

Griseofulvin is well absorbed and absorption is enhanced if taken with a high-fat meal. In children, it may be given with milk. A 1000-mg dose produces a peak serum level of about 1–2 mg/L after 4 h, with a half-life of at least 9 h. An ultra-fine preparation of griseofulvin exists which is almost totally absorbed and permits the use of lower doses (typically 330–660 mg daily). This preparation is not available in the UK. Elimination is mainly through the liver and inactive metabolites are excreted in the urine. Less than 1% of a dose is excreted in urine in the active form, but some active drug is excreted in the faeces.

The duration of treatment with griseofulvin is dependent entirely on clinical response. Skin or hair infection usually requires 4–12 weeks' therapy, but nail infections respond much more slowly; 6 months' treatment is often required for fingernails, a year or more for toenail infections. Unfortunately, the rate of treatment failure or relapse in nail infection is high, and may reach up to 60%. Hence, terbinafine and itraconazole may be preferred agents.

Pityriasis versicolor

This is a common superficial skin infection caused by a yeast-like fungus, *Malassezia furfur*. The organism is a member of the normal skin flora and lives only on the skin because it has a growth requirement for medium-chain fatty acids present in sebum.

Clinical presentation

The condition usually appears as patches scattered over the trunk, neck and shoulders. These patches produce scales and may be pigmented in light-skinned individuals, appearing light brown in colour. In dark-skinned patients, the lesions may lose pigment and appear lighter than normal skin.

In some patients, Malassezia yeast is also associated with dandruff and seborrhoeic dermatitis, although the exact role of the yeast in causing this condition remains uncertain. In AIDS patients, seborrhoeic dermatitis may be quite extensive and sudden in onset.

Malassezia folliculitis can appear as greasy papules or pustules on the trunk or face of an HIV-infected individual.

Diagnosis

The diagnosis is made by microscopy of scrapings from the lesion. The specimen is examined for the presence of yeast cells and short hyphae. Culture is not usually required for diagnosis and, since it requires special culture media, is not routinely attempted.

Treatment

Pityriasis versicolor is treated with topical terbinafine cream or a topical imidazole cream such as clotrimazole, econazole or miconazole. Cheaper topical alternatives are 2% selenium sulphide lotion or 20% sodium thiosulphate applied daily for 10–14 days. Relapses are common and treatment may need to be repeated. In severe cases, oral itraconazole (200 mg once daily for 7 days) may be given. Treatment of seborrhoeic dermatitis and folliculitis is undertaken with topical azole creams and 1% hydrocortisone. This condition can also often relapse.

Ear infection

Fungi sometimes infect the external auditory canal, causing otitis externa, the most common causative organisms being various species of *Aspergillus* (such as *A. niger* and *A. fumigatus*) and *Candida albicans* and other *Candida* species. A variety of other fungi found in the environment can also cause this condition. The use of topical antibacterial agents in the ear may predispose to local fungal infection.

Clinical presentation

Fungal infection of the ear usually presents as pain and itching in the auditory canal, sometimes with a reduction in hearing due to blockage of the canal. There may be an associated discharge from the ear. Clinical examination shows a swollen red canal, and the fungal mycelium is sometimes visible as an amorphous white or grey mass.

Diagnosis

The diagnosis of a fungal infection of the external canal can be made by microscopy and culture of material obtained from the ear.

Treatment

Aural toilet with removal of obstructing debris is very important in the management of fungal infections of the external auditory canal. A topical antifungal agent such as nystatin or amphotericin, or an imidazole can also be applied.

Infections with saprophytic fungi

Some saprophytic fungi (normally harmless human commensals) can cause significant infections. An example of such an infection in a host with a normal immune system is fusarium keratitis in contact lens wearers. *Penicillium marneffei* can cause skin infection and disseminated fatal infection in HIV-infected patients in South East Asia. *Scedospermium* pulmonary infections are seen in lung transplant recipients.

A large retrospective data from the USA revealed that the three most common non-Aspergillus moulds causing invasive fungal infection among patients receiving haemopoietic stem cell transplants (HSCT) were *Fusarium*, *Scedospermium* and *Zygomycetes*.

Deep-seated fungal infections

Most deep-seated or systemic fungal infections seen in the UK are the result of some breakdown in the normal body defences, which may be due to disease or medical treatment. Fungi that cause superficial infections can also cause deep-seated infection in immunocompromised patients with leukaemia and lymphoma and those in the post-transplant period of immunosuppression. There are, however, a group of fungi, often referred to rather misleadingly as the pathogenic fungi, which are able to cause systemic infection in a previously healthy person. These infections, which are usually due to dimorphic fungi, include diseases such as histoplasmosis, blastomycosis and coccidioidomycosis. They are rare in the UK but rather more common in the USA and other parts of the world.

Fungal infections in the compromised host

Common mycoses

Epidemiology and predisposing factors

There are a large number of conditions which may predispose the individual to systemic or deep-seated fungal infection. These are summarised in Table 42.4. A breach in the body's mechanical barriers may predispose to fungal infection. For example, fungal infection of the urinary tract occurs most commonly in catheterised patients who have received broad-spectrum antibiotics, while total parenteral nutrition (TPN) is strongly associated with fungaemia, sometimes with unusual fungi such as *Malassezia furfur*. This is due to the use of TPN infusions containing lipids, which are a growth requirement of this organism. Most cases of systemic fungal infection, however, are associated with a defect in the patient's immune system, and the nature of the organisms encountered is often related to the nature of the immunosuppression. Neutropenia, for example, is usually associated with *Candida* species, *Aspergillus* and mucormycosis, while defects of cell-mediated immunity, for example HIV infection, are strongly associated with infection by *Cryptococcus neoformans*. Prolonged diabetic ketoacidosis is a risk factor for developing rhinocerebral zygomycosis where mortality can be as high as 100% if there is significant underlying disease.

Many different fungi have been described as causing systemic fungal infection, but the most common organisms encountered and the conditions they cause are listed in Table 42.5. Of these, *Candida* and *Aspergillus* are by far the most common in the UK.

Table 42.5 Common causes of systemic and deep-seated fungal infection in the UK

Condition/organism	Common clinical presentations
Candidiasis (*Candida albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, other *Candida* species)	Fungaemia Colonisation of intravenous cannulae Pneumonia Meningitis Bone and joint infections Endocarditis Endophthalmitis Peritonitis in chronic ambulatory peritoneal dialysis
Aspergillosis (*Aspergillus fumigatus*, *A. flavus*, other *Aspergillus* species)	Invasive pulmonary aspergillosis Disseminated aspergillosis Aspergilloma Endocarditis
Cryptococcosis (*Cryptococcus neoformans*)	Meningitis Pneumonia Cutaneous infection
Zygomycosis (various species of the genera *Rhizopus*, *Mucor*, *Absidia*)	Rhinocerebral infection Pulmonary mucormycosis Surgical wound and burns infection
Malassezia furfur	Cutaneous infection (especially in burns patients) Fungaemia associated with total parenteral nutrition

Clinical presentation

Symptoms can be non-specific like low-grade fever, night sweats, weight loss, cough, chest pain and septic shock in extreme cases (Table 42.6).

Diagnosis

Organ-specific radiological findings backed by laboratory tests, as discussed earlier in this chapter, are the mainstay of diagnosis.

Treatment

Compared to the vast array of antibacterial agents available to treat bacterial infections, there are very few systemic antifungal agents available and these comprise four major categories: the polyenes (conventional and lipid formulations of Amphotericin B), the triazoles (fluconazole, itraconazole, voriconazole and posaconazole), the echinocandins (caspofungin, anidulafungin and micafungin) and flucytosine. To provide optimal therapy to the patient, it is necessary to understand the profile, properties and toxicity of these agents. Table 42.7 details the antifungal spectrum of activity against common fungi.

Antifungal prophylaxis is commonly used to prevent invasive fungal infections in the 'at risk' group of patients.

Amphotericin B

Amphotericin, a member of the polyene group, is obtained from various species of *Streptomyces*. Chemically, it is a large carbon ring of 37 carbon atoms closed by a lactone bond. One

Table 42.6 Clinical presentation of systemic fungal infection

Condition	Clinical presentation
Fungaemia (the presence of fungi in the bloodstream), usually due to *Candida* species	Fever, low blood pressure and sometimes other features of septic shock, especially in neutropenic patients Relatively low-grade fungaemias such as those associated with colonised intravenous cannulae often present only with fever Disseminated infection to multiple organ systems is quite common with *Candida* species, leading to central nervous system disease, endocarditis, endophthalmitis, skin infections, renal disease, bone and joint infection
Pneumonia, most frequently due to *Aspergillus* species	Fever, chest pain and cough which may be non-productive. May progress rapidly, especially with *Aspergillus* infection, to severe respiratory distress, necrosis of the lung and pulmonary haemorrhage Formation of fungal balls in pre-existing lung cavities with or without invasion
Meningitis and other central nervous system infection	*Candida* infection may present as a typical meningitis, although it is often more insidious. Aspergillosis is associated with headache, confusion and focal neurological signs due to the presence of brain infarcts. Cryptococcosis most frequently presents as a chronic, insidious meningitis with headache and alteration in mental state
Mucormycosis	Angioinvasive. The most common presentation of mucormycosis is rhinocerebral infection. Initially an infection of the sinuses, it then spreads locally to the palate, orbit and eventually into the brain, leading to encephalitis Pulmonary disease can present as fungal balls radiologically with symptoms of haemoptysis

Table 42.7 Antifungal spectrum of activity against common fungi (adapted from Dodds Ashley et al., 2006)

	Antifungal agent								
Organism	AmB[a]	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Aspergillus species	+	–	+	+	+	+	+	+	–
A. flavus	±	–	+	+	+	+	+	+	–
A. fumigatus	+	–	+	+	+	+	+	+	–
A. niger	+	–	±	+	+	+	+	+	–
A. terreus	–	–	+	+	+	+	+	+	–
Candida species	+	+	+	+	+	+	+	+	+
C. albicans	+	+	+	+	+	+	+	+	+
C. glabrata	+	±	±	+	+	+	+	+	+
C. krusei	+	–	±	+	+	+	+	+	±
C. lusitaniae	–	+	+	+	+	+	+	+	±
C. parapsilosis	+	+	+	+	+	±	±	±	+
C. tropicalis	+	+	+	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	+	–	–	–	+
Coccidioides species	+	+	+	+	+	±[b]	±[b]	±[b]	–
Blastomyces	+	+	+	+	+	±[b]	±[b]	±[b]	–
Histoplasma species	+	+	+	+	+	±[b]	±[b]	±[b]	–
Fusarium species	±	–	–	+	+	–	–	–	–
Scedosprium apiospermum	±	–	±	+	+	–	–	–	–
Scedosporium prolificans	–	–	–	±	±	–	–	–	–
Zygomycetes	±	–	–	–	+	–	–	–	–

Note: Plus signs (+) indicate that the antifungal agent has activity against the organism specified. Minus signs (–) indicate that the antifungal agent does not have activity against the organism specified. Plus-minus signs (±) indicate agent has variable activity against the organism specified. AmB, amphotericin B; Flu, fluconazole; Itr, itraconazole; Pos, posaconazole; Vor, voriconazole.

[a]Includes lipid formulations.

[b]*In vitro* data show that the echinocandins (specifically, micafungin) may have variable activity against the dimorphic fungi, depending on whether they are in the mycelial or yeast-like form.

side of the molecule contains seven carbon- to-carbon double bonds (polyene) and the other side contains seven hydroxyl groups. It dissolves in organic polar solvents but forms a colloidal suspension of micelles in water which is rendered stable by the addition of the surfactant sodium deoxycholate.

Mode of action. Amphotericin B binds to the ergosterol in fungal cell membrane affecting its integrity by forming pores and therefore cell death. Nystatin, the other polyene, is only used topically because of toxicity associated with its systemic use.

Spectrum of activity. Amphotericin is active against a vast majority of fungi and this is the same for all formulations. Development of resistance is uncommon, although primary resistance has been identified for *Aspergillus terreus*, *Scedosporium* spp., *Trichosporon* spp. and *Candida lusitaniae.*

Pharmacodynamically, the ratio of the peak serum concentration to the MIC is important for its efficacy.

Amphotericin B deoxycholate (ABD). Released in 1950, colloidal in nature, amphotericin B deoxycholate is highly protein bound (99%) and insoluble in water. It penetrates poorly into cerebrospinal fluid. Initial elimination of the drug occurs with a half-life of 24–48 h, but this is followed by very slow elimination (half-life about 14 days). As a consequence, it may take 10 weeks for the drug to disappear from the circulation.

Amphotericin B deoxycholate is given by slow IV infusion in 5% dextrose with a dose range of 0.3–1 mg/kg increased to 1.5 mg/kg for serious invasive infections. The duration of treatment can vary from 1 to 2 weeks to longer, depending on the severity of the infection and the organ system involved.

Adverse effects. Nephrotoxicity is the most serious side effect of amphotericin. Renal failure should be monitored regularly at least every other day, and if the serum creatinine exceeds 250 µmol/L, the drug should be discontinued until the creatinine level falls below this limit. Hypokalaemia is also a problem and may be severe, necessitating replacement therapy.

Azotaemia may be seen in patients after the first few infusions of amphotericin B deoxycholate. Chills, fever and tachypnoea may occur but can be avoided by addition of hydrocortisone 25–50 mg to the infusion solution.

The manufacturer recommends that before commencing treatment, a 1 mg test dose should be given in 50 ml of 5% dextrose over a 1- to 2-h period and the patient monitored for fever, rigors and hypotension. True allergic reactions are rare.

Amphotericin B lipid formulations

The advantage of delivering amphotericin encapsulated in liposomes or as a complex with lipid molecules is that a higher unit dose can be given and there is reduction in toxic effects. Three such preparations are currently available: liposomal amphotericin B (AmBisome®), amphotericin B lipid complex (Abelcept®) and amphotericin B colloidal dispersion (Amphocil®).

Liposomal amphotericin B. In liposomal amphotericin B (AmBisome®), the drug is contained in small vesicles each consisting of a phospholipid bilayer enclosing an aqueous environment. This permits the delivery of higher doses (3 mg/kg is recommended, but doses up to 10 mg/kg have been used in some centres) compared to conventional amphotericin, with very little of the immediate toxicity which is such a problem with the conventional formulation. Higher peak serum concentrations are obtained with the liposomal formulation compared to equivalent doses of the conventional drug, although it is not certain if this is clinically relevant. Liposomal amphotericin is concentrated mainly in the liver and spleen, where it is taken up by cells of the reticuloendothelial system. Concentrations in the lung and kidneys are much lower, which may or may not be clinically important.

There is reduced nephrotoxicity with this formulation, and some of the renal dysfunction which has been described in clinical trials of liposomal amphotericin may have been due to concomitant drugs. Three randomised, comparative clinical trials of liposomal amphotericin versus conventional amphotericin B have shown reduced toxicity due to the liposomal preparation, and there is additional evidence for this from open studies. It is this comparative lack of toxicity which accounts for much of the popularity of this agent, despite its expense. These studies also indicate that this agent performs as well as the conventional preparation in febrile neutropenic patients.

Amphotericin B lipid complex and amphotericin B colloidal dispersion. Amphotericin B lipid complex (Abelcet®) is not a liposomal formulation, but consists of large sheets of amphotericin combined with phospholipids. This formulation gives lower peak serum levels compared to the conventional drug because it is rapidly taken up by tissue macrophages, while concentrations in the lungs and the liver are much higher. Patients seem to experience more immediate side effects than with liposomal amphotericin. There is less clinical trial evidence for the use of this agent compared to the liposomal preparation. Amphotericin B colloidal dispersion (Amphocil®) is a formulation consisting of tiny discs of amphotericin and cholesterylsulphate. Like the lipid complex, it too produces low peak serum levels but high liver concentrations compared to the conventional drug. There is less clinical experience with this preparation than with the liposomal preparation, and it appears to have a higher incidence of certain adverse reactions than conventional amphotericin.

Choosing a lipid preparation. Unfortunately, there are limited comparative trial data between the different lipid formulations. At present, the greatest clinical experience is with liposomal amphotericin B and by reason of this and the reduced incidence of side effects, it is the preferred agent of the three in many centres in the UK. In an ideal world, all patients requiring amphotericin would receive the conventional preparation initially, being changed to a lipid formulation only if they fail to respond to or cannot tolerate the side effects of the conventional form. However, the incidence of side effects and the difficulty in administration of conventional amphotericin have in practice led to its replacement in most centres with a lipid formulation.

Flucytosine

Amphotericin B and griseofulvin were the only systemic antifungal agents available until the early 1970s, when flucytosine became available for patient use.

Mode of action. Flucytosine (5-fluorocytosine) is a synthetic fluorinated nucleotide analogue. The mode of action is twofold. Following uptake by the cell, which is dependent on the presence of cytosine permease, flucytosine is deaminated to 5-fluorouracil by cytosine deaminase. This in turn is incorporated into fungal RNA in place of uracil, leading to impairment of protein synthesis. Further metabolism of 5-fluorouracil leads to a metabolite that inhibits the enzyme thymidylate synthetase, leading to inhibition of DNA synthesis. Mammalian cells have absent or weak cytosine deaminase activity which accounts for the selective toxicity of flucytosine.

For all practical purposes, flucytosine is only active against yeasts and yeast-like fungi. Inherent resistance occurs in approximately 10% of clinical isolates of *Candida* species, and acquired resistance develops rapidly if the drug is used alone.

There are several resistance mechanisms, some of which result from a single-step mutation giving a high frequency of acquired resistance in organisms exposed to the drug. For this reason, flucytosine should always be given in combination with another agent such as amphotericin, with which it is synergistic.

Pharmacokinetics. Flucytosine is highly soluble in water and over 90% of an oral dose is absorbed from the gastro-intestinal tract. Virtually all the absorbed dose is excreted unchanged in the urine by glomerular filtration. The elimination half-life is about 4 h, but this is greatly prolonged in renal failure and dosage modification is required in patients with renal dysfunction. The degree of protein binding is very low and flucytosine penetrates well into all tissues, including the aqueous humour of the eye, where about 10% of the serum level is achieved, and the CSF, where about 80% of the serum level is achieved.

Administrations. Flucytosine is given orally or by short intravenous infusion. The dose administered by either route in patients with normal renal function is 100–200 mg/kg/day in four divided doses. This must be reduced in renal failure, but the degree of reduction depends on the degree of renal impairment and it is obligatory to monitor the serum levels of flucytosine. Unfortunately, flucytosine assay is now rarely carried out routinely in UK laboratories. Flucytosine is usually given in conjunction with amphotericin which will probably cause some degree of renal dysfunction, so requiring modification of the flucytosine dose. To avoid dose-related marrow toxicity, the peak serum level, obtained at 1 h after an intravenous dose or 2 h after an oral dose, should be maintained in the range 70–80 mg/L and should not be allowed to exceed 100 mg/L.

Side effects. Some of the side effects of flucytosine are given in Table 42.3. The most important toxic effect is a dose-related myelosuppression with neutropenia and thrombocytopenia. This is usually reversible and can be avoided by monitoring serum levels of flucytosine and adjusting the dose accordingly. Hepatotoxicity is also probably a result of high serum levels, and liver function tests should be performed regularly. The drug is teratogenic in some animals and is not recommended in pregnant women for relatively trivial infections such as a fungal urinary tract infection. In cases of a life-threatening fungal infection, which is very rare in pregnancy, the potential benefits of flucytosine must be weighed against the possible risks.

Imidazoles

The imidazoles clotrimazole, econazole, fenticonazole, sulconazole and tioconazole are now principally used for the local treatment of vaginal candidiasis and for dermatophyte infections. Ketoconazole, which first became available in 1979, can be administered for systemic use, but even this agent has been superseded by the triazoles.

Triazoles

Three triazoles are licensed in the UK: fluconazole, itraconazole and voriconazole. They differ substantially from one another in their pharmacokinetic and antifungal activity (Table 42.8). Their main side effects are listed in Table 42.3.

The basic chemical structure of the triazoles is the azole ring, a five-membered ring containing three nitrogen atoms. Their principal mode of action involves one of the nitrogen atoms of the azole ring binding to fungal cytochrome P450 enzymes. This inhibits the demethylation of lansterol and leads to a reduced concentration of ergosterol necessary for a normal fungal cytoplasmic membrane. The propensity, in man, to also inhibit the metabolism of drugs by cytochrome P450 results in a considerable number of drug interactions.

Fluconazole

Clinical use. Fluconazole is available both orally and parenterally and is used only in the treatment and prophylaxis of infections due to yeasts and yeast-like fungi. It is not used for the treatment of infections due to moulds. It is highly effective in the treatment of *Cryptococcus* infection, but the first-line treatment of cryptococcosis of the central nervous system is the combination of amphotericin B plus flucytosine for CNS infection due to this organism. This may be followed by fluconazole, which in HIV-infected patients will be required life long as suppressive treatment to prevent relapse. In immunocompetent hosts, fluconazole may be used as the primary treatment for disease not involving the CNS, such as pulmonary infection.

In patients with candidaemia due to colonised intravenous cannulae, the most important treatment is removal of the infected cannula, but it is common practice to give a short course of antifungal therapy to prevent disseminated infection elsewhere. Although not proven in randomised clinical trials, changing potentially infected central-line catheters in candidaemia patients is probably the most important part of therapy.

In non-neutropenic patients, studies have shown fluconazole and caspofungin to be as efficacious as, and less toxic than, conventional amphotericin B. In such patients, where the infecting organism and its susceptibility to fluconazole are known, it would be reasonable to commence treatment with fluconazole; caspofungin is a potential alternative. In neutropenic patients, and in patients infected with fluconazole-resistant organisms, amphotericin continues to be the treatment of choice. Fluconazole has also been successfully used as prophylaxis against *Candida* infections in neutropenic patients and patients with AIDS, but this in turn has been associated with an increasing incidence of systemic infections with fluconazole-resistant strains.

Resistance. Some units that use fluconazole extensively have noted an increase in the isolation of yeasts resistant to the drug, with the prevalence of resistance related to the extent of use of fluconazole. Resistance in *Candida* species is mainly seen in patients who are given long-term prophylactic fluconazole. This selects out those *Candida* species such as *C. krusei* and *C. glabrata* that are inherently less susceptible to fluconazole. Resistance in *C. albicans*, the most common species infecting humans, is seen mainly in AIDS patients, partly due to the extensive use of fluconazole in treating severe oral and pharyngeal candidiasis in such patients and partly due to the very large numbers of yeasts in the oropharynx of AIDS patients with candidiasis, which increases the chance of resistance due to spontaneous mutation.

Table 42.8 Comparative pharmacokinetics of antifungal agents (adapted from Dodds Ashley et al., 2006)

	Antifungal agent											
Pharmacokinetic parameter	AmB	ABCD	ABLC	LAB	Flu	Itr[a]	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Oral bioavailability (%)	<5	<5	<5	<5	95	50	96	ND	<5	<5	<5	80
Food effect	NA	NA	NA	NA	NE	ES	ES	Food	NA	NA	NA	NE
Distribution												
Total C_{max} µcg/mL	0.5–2	4	131	0.1	0.7	11	4.6	7.8	0.83	0.27	0.24	80
AUC, mg x h/L	17	43	14	555	400	29.2	20.3	8.9	99[b]	119	158[b]	62
Protein binding (%)	>95	>95	>95	>95	10	99.8	58	99	84	97	99	4
CSF penetration (%)	0–4	<5	<5	<5	>60	<10	60	NR	<5	<5	<5	75
Vitreal penetration (%)	0–38[c,d]	0–38[c,d]	0–38[c,d]	0–38[c,d]	28–75[c,d]	10[c]	38[c]	26[c,d]	0[d]	0[c]	<1[d]	49[d]
Urine penetration (%)[e]	3–20	<5	<5	4.5	90	1–10	<2	<2	<2	<2	<2	90
Metabolism	Minor Hep	Unk	Unk	Unk	Minor Hep	Hep	Hep	Hep	None	Hep	Hep	Minor intestinal
Elimination	Faeces	Unk	Unk	Unk	Urine	Hep	Renal	Faeces	Faeces	Urine	Faeces	Renal
Half-life (h)	50	30	173	100–153	31	24	6	25	26	30	15	3–6

Note: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB amphotericin B; AUC, area under the concentration curve; C_{max} peak drug concentration; ES, empty stomach; Flu, fluconazole, Hep, hepatic; Itr, itraconazole; LAB, liposomal amphotericin B; NA, not applicable; ND, no data; NE, no effect; Pos, posaconazole; Unk, unknown; Vor, voriconazole.

[a]Data are for oral solution.

[b]For doses of 100 mg/day.

[c]Human.

[d]Animal.

[e]Percentage of active drug or metabolites.

Itraconazole

Itraconazole is available for both oral and intravenous use. The drug was originally available in capsules, but a newer liquid formulation gives better absorption and pharmacokinetic profile than the original capsule preparation, leading to significantly greater bioavailability and higher serum levels. Systemic bioavailability of itraconazole oral solution is around 55% optimised under fasting conditions. Itraconazole is extensively metabolised by the liver, predominantly by the CYP 3A4 isoenzyme system and is known to undergo enterohepatic circulation. This is a broad-spectrum antifungal which is effective against yeasts, dermatophytes, the 'pathogenic' fungi and some filamentous fungi, such as *Aspergillus*.

Clinical use. In deep-seated infection, itraconazole is used to treat infections due to the 'pathogenic' fungi, but there is less published evidence of its use in the treatment of systemic candidiasis and it cannot be recommended for this purpose (Maertens and Boogaerts, 2005). However, it may be useful in patients who are infected with strains resistant to fluconazole, some of which may remain sensitive to itraconazole, and in patients who are for some reason unable to tolerate fluconazole. It has also been used to treat cryptococcosis, despite its poor penetration of cerebrospinal fluid, and in that condition, it is an alternative to fluconazole for patients who cannot take the latter drug. However, one study comparing fluconazole and itraconazole as maintenance treatment for cryptococcosis was discontinued due to the high rate of relapse in the itraconazole arm.

There is now considerable evidence to support the use of itraconazole as a prophylactic agent in immunocompromised patients. It has been shown to be effective in reducing the incidence of systemic fungal infection compared to placebo and to be more effective than fluconazole, although this is due to a greater reduction in infections due to filamentous fungi, including *Aspergillus*.

Voriconazole

Voriconazole is available for both oral and intravenous administration. It has advantages over itraconazole in that its absorption from the gastro-intestinal tract is significantly better and is not affected by reductions in gastric acidity due to disease or concomitant medication. Its spectrum of activity is similar to that of itraconazole, but it is more active against *Fusarium* species, a mould which causes superficial infection of the nails and cornea, and occasionally systemic infection in immunocompromised patients.

Pharmacokinetics. Voriconazole given orally is rapidly and almost fully absorbed (oral bioavailability > 90%) with a maximum serum concentration being achieved in about 2 h after administration under fasting conditions. It is extensively distributed into tissue and penetrates well into the CSF and into vitreous and aqueous humour. It is cleared by hepatic cytochrome P450 metabolism and is involved in many clinically relevant drug–drug interactions. Therapeutic drug monitoring may be indicated in some clinical settings.

Clinical use. The main clinical indication for the use of voriconazole is aspergillosis. Studies have shown improved efficacy compared to conventional amphotericin B in systemic *Aspergillus* infection. The largest randomised control trial demonstrates that voriconazole is superior to amphotericin B deoxycholate as primary therapy of Aspergillosis (Walsh et al., 2008). One particular indication is cerebral aspergillosis. Although rare, this carries a high mortality rate (90% or higher), and one study has shown this to be reduced by voriconazole, presumably due to its better penetration into the central nervous system. In addition to aspergillosis, voriconazole is also licensed for the treatment of *Fusarium* infection and for the management of patients infected with strains of *Candida* resistant to fluconazole. It has been shown to be as efficacious as amphotericin B followed by fluconazole in the treatment of candidaemia in patients who were not neutropenic, but it is not licensed for this indication.

Administration. For invasive pulmonary aspergillosis, a loading dose of 6 mg/kg IV every 12 h for 2 doses was given followed by 4 mg/kg every 12 h and converted to oral therapy 200 mg every 12 h depending on clinical review to decide duration of treatment.

Side effects. Voriconazole has a side-effect profile similar to that of other triazoles. Two adverse effects associated with voriconazole are visual disturbance (appearance of bright lights, colour changes or wavy lines) in 45% of patients and cutaneous phototoxicity (rash) in 8% patients. Both side effects are reversible after discontinuation of therapy.

Posaconazole

Posaconazole is the latest triazole to be licensed in the UK. Like itraconazole, it is absorbed slowly, is a highly protein bound (>98%) and reaches a steady state after a period of 7–10 days. Optimal absorption is achieved when taken with a high fatty meal.

Clinical use. Posaconazole is used 200 mg three times daily for prophylaxis of invasive fungal infection during neutropenia or moderate to severe graft versus host disease (GVHD).

Caspofungin

Caspofungin was the first of the echinocandins to become available for routine use, and others, such as micafungin and anidulafungin, have only recently become available. These agents interfere with the production of the fungal cell wall by inhibiting the synthesis of an important component, 1,3-ß-D-glucan. This is a target which does not exist in mammalian cells, providing selective toxicity against fungi. Caspofungin has a significant advantage over the triazoles in that it does not inhibit the cytochrome P450 system and therefore is not associated with such a wide range of drug interactions.

Susceptible fungi. The drug has a rather unusual spectrum of activity. It is active against most species of *Candida*, although some are less susceptible than others, but *Cryptococcus* is resistant. The commonly encountered species of *Aspergillus* are susceptible, but the drug is inactive against the dermatophytes and activity against other fungi is variable.

Clinical use. Caspofungin is only available for administration via the intravenous route and does not penetrate into the cerebrospinal fluid. Due to its spectrum of activity, caspofungin is indicated only for candidiasis and aspergillosis. A comparative study showed caspofungin to be as efficacious as conventional amphotericin B in invasive candidiasis. It has been shown to be effective in patients with aspergillosis who failed to respond to, or who could not tolerate, other antifungal agents. Finally, caspofungin was also shown to be as effective as liposomal amphotericin B in the empirical treatment of fungal infection in neutropenic patients and had a lower incidence of unwanted effects (Walsh et al., 2004). In the UK, the drug is licensed for this indication.

Choice of treatment

A recent development has been the use of combinations of antifungal agents to improve on the results of single agents. At the present time, there is little firm evidence to support the use of such combinations. Amphotericin B plus flucytosine in the treatment of cryptococcosis is the only combination where evidence exists of increased efficacy over either agent alone. However, faced with a seriously ill patient not responding to single agents, it is not surprising that many clinicians attempt the use of a combination of antifungals, even though the evidence is that the results are no better than monotherapy.

Practice points regarding the drug toxicity in systemic antifungal agents are detailed in Table 42.9.

Table 42.9 Practice points

Drug toxicity in systemic antifungal agents	
Infusion-related side effects	• Particularly with conventional amphotericin B • Lipid-based preparations also show these, but to a lesser extent
Nephrotoxicity	• Particularly with conventional amphotericin B • Results in renal dysfunction • Cessation of treatment may be required • Drug-level monitoring is not helpful in prevention • Potassium loss and hypokalaemia are a serious complication • Renal toxicity may be potentiated by concomitant nephrotoxic agents
Hepatotoxicity	• Associated with the azole antifungals • Was particularly severe with ketoconazole • The newer triazoles may also cause serious liver damage
Bone marrow suppression	• Associated with flucytosine • Dose-related problem, so drug-level monitoring may help to prevent it • Tends to preclude the use of flucytosine in patients whose marrow is already damaged (e.g. in haematological malignancy or following bone marrow transplant)
Drug interactions	• Associated particularly with the azoles • Due to their mode of action in inhibiting the cytochrome P450 system • A wide range of drugs may be affected, some with serious interactions
Difficulties in drug administration	
Drug precipitation	• Amphotericin B will precipitate out if given in electrolyte-containing infusions • This may also happen in 5% dextrose due to acidity resulting from the manufacturing process
Need for a test dose	• Required for all amphotericin B preparations
Long infusion times and/or large infusion volumes	• A particular problem with conventional amphotericin • Long infusion times mean reduced access to intravenous cannulae for other purposes • Large infusion volumes may be undesirable in patients with renal or cardiac dysfunction
Variable absorption when taken by mouth	• A known problem with itraconazole • Absorption is reduced in the presence of raised gastric pH (e.g. following the use of antacids or drugs such as omeprazole) • Absorption is increased in the presence of food or if taken with a cola drink • Subtherapeutic levels may occur due to poor absorption • Therapeutic drug monitoring is recommended to avoid low levels

Continued

Table 42.9 Practice points—cont'd

Resistance to antifungal agents	
Amphotericin B	• Usually seen as a very broad-spectrum antifungal, but inherent resistance is seen in several clinically significant species: *Aspergillus terreus* *Candida lusitaniae* *Scedosporium apiospermum* • Acquired resistance developing during treatment is very uncommon • Lipid preparations have identical *in vitro* antifungal activity to the conventional form
Flucytosine	• Acquired resistance during treatment is very common in *Candida* species • Monotherapy promotes the rapid development of resistance • Combination therapy with amphotericin will reduce the possibility of acquired resistance developing during treatment
Fluconazole	• Some species of *Candida* are inherently resistant or less susceptible to fluconazole: *C. krusei* *C. glabrata* • Long-term use of fluconazole may result in increased infections with these more resistant strains • Long-term use may also result in reduced susceptibility in strains of *C. albicans*

Case studies

Case 42.1

A 27-year-old woman visits her primary care doctor complaining that her toenails have become distorted and discoloured. Since it looks unattractive, she would like it corrected before her summer beach holiday. The primary care doctor makes the clinical diagnosis of tinea unguium (dermatophytosis of the nail) which is confirmed by laboratory culture of nail scrapings. The doctor knows that this condition is unlikely to respond to topical treatment and therefore consults the British National Formulary for a systemic agent. He finds that griseofulvin, terbinafine and itraconazole are all available for this condition. However, the situation is complicated by the fact that his patient tells him that she is trying to get pregnant and does not want to take anything which might harm a baby. At this point, the doctor seeks specialist advice.

Question

What is the most appropriate (and safe) treatment in this patient?

Answer

This is a difficult issue. Griseofulvin is contraindicated, due to its known teratogenicity in animals. In addition, this drug decreases the effectiveness of oral contraceptives, so it would not be appropriate to give it along with an oral contraceptive agent to prevent pregnancy during use. It is also recommended that oral contraception be continued for at least a month after discontinuing griseofulvin. Therefore, in this patient, it is not an appropriate choice.

The position of itraconazole is a little different. Like griseofulvin, it has the U.S. Food & Drugs Administration (FDA) category C (studies show fetal harm in animals, but evidence in human beings is lacking), but there is at least one report of almost 200 women given itraconazole in the first trimester of pregnancy without evidence of fetal harm. In the current state of knowledge, however, it would be difficult to recommend itraconazole to this patient.

Terbinafine carries FDA category B (no evidence in animal studies of fetal harm, but studies proving safety in pregnant women are not available). Therefore, it could be given to the patient if the benefit outweighs the risk, but since this is not a serious condition, this approach would be difficult to justify.

After some discussion, the patient decided that she wanted the condition treated more than she wanted to become pregnant, so she opted to take a course of terbinafine but return to using her oral contraception until the treatment course was complete.

Case 42.2

A 56-year-old diabetic male with carcinoma of the oesophagus undergoes sub-total oesophagectomy. He spends the early post-operative period on surgical ITU and is sent to the surgical ward for further management. On day 6, post-op, he begins to show signs of sepsis for which antibiotics are commenced. However, 48 h later, he has difficulty in breathing, takes a turn for the worse and is transferred to ITU. Imaging the chest revealed a leak from the oesophagectomy site and fluid collection in the pleural space. Gram stain of aspirated pleural fluid revealed budding yeast cells and sputum culture taken 2 days previously has grown *Aspergillus*.

Question

How should this patient's infection be managed?

Answer

The immediate management of this patient would involve drainage of pleural fluid through an intercostal drain and systemic antifungal therapy. The source is very likely to be oral thrush as the patient is diabetic and the candida has travelled from the mouth/oropharynx through the leak in the oesophagectomy wound into the pleural space. Fluconazole at 400 mg twice daily should be commenced awaiting full culture identification of the yeast and antifungal sensitivities. Urgent review is indicated for surgical intervention to close the leak. The duration of antifungal agent would be normally be 14–21 days.

Re-collection of yeasts in inadequately treated spaces can be a problem. It may be useful to add a second antifungal agent to fluconazole. The presence of *Aspergillus* in sputum may be an environmental contamination; therefore, a second specimen will be needed to confirm.

Aspergillus is not sensitive to fluconazole, in which case amphotericin B or voriconazole may be indicated.

Case 42.3

A 18-year-old boy with acute myeloblastic leukaemia sustained 20% accidental burns injury on face, upper body and right arm at a family barbecue. He had recently left hospital after successful antibiotic treatment for a febrile neutropenic episode post-chemotherapy.

Two weeks after admission to ITU for management of burns, he undergoes a septic episode with septic shock. A blood culture taken through a central line shows Gram-negative bacilli. He is commenced on broad-spectrum antibiotics. His peripheral blood count is 3 × 10^9/L and he has a markedly raised C-reactive protein (CRP). The patient has suffered a moderate degree of renal failure. Two days later, another blood culture is taken through an arterial line and shows yeast cells on Gram stain. Intravenous fluconazole is added to his treatment. Culture growth from the central line blood culture reveals *Pseudomonas aeruginosa* and *Candida albicans*. The arterial blood culture grows *Candida krusei*. Antifungal sensitivities are awaited.

Question

How should the patient be managed?

Answer

Treatment of infections in burns patients can be challenging as the loss in skin integrity increases the risk of being colonised with various endogenous and hospital-acquired bacteria and fungi. Patients with haematological malignancies and chemotherapy treatment are more vulnerable to opportunistic infections, and this case has an additional co-morbidity on top.

Ideally, antibiotics should be avoided in a patient who has an invasive fungal infection as it is believed that killing the bacterial flora helps fungi thrive in the absence of commensal competition. In this case, the patient has concomitant Gram-negative sepsis and lacks a strong bodily defence system because of his underlying disease condition.

Candida krusei is known to be resistant to fluconazole. It is difficult to treat intravenous catheter and other line infections with systemic antibiotics and antifugals alone. It is imperative that these lines are taken out, and treatment given through temporary peripheral lines for at least 48 h before a new central line is inserted. New lines are very likely to get colonised with the same microorganisms if inserted too early. Both *Candida albicans* and *Candida krusei* can be treated with a lipid formulation of amphotericin (use of non-lipid conventional formulations of amphotericin should be avoided as the patient has a moderate degree of renal failure and his present condition could deteriorate).

The duration of treatment can be decided based on daily clinical follow-up that includes imaging and echo cardiograms for up to 2 weeks to look for seeding of *Candida* in other organs. Choice of antifungals can be reviewed after antifungal sensitivity is made available and amphotericin can be switched to caspofungin if necessary.

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Thyroid and parathyroid disorders 43

M.D. Page

Key points

- When diagnosing thyroid conditions, the possibility of drug-induced disease should always be considered.
- The treatment of hypothyroidism requires lifelong thyroxine therapy and monitoring.
- Thyroxine replacement therapy should be introduced cautiously in the elderly, particularly those with cardiac disease.
- Thyroxine replacement therapy can be given weekly in patients who forget their daily doses or who are unable to self-medicate.
- Thyrotoxicosis can be treated with thionamide therapy, radioiodine or surgery. The choice will largely be determined by the age of the patient, the cause of the thyrotoxicosis, the severity of the condition, co-morbidity and patient preference.
- Patients treated with thionamide therapy require careful counselling about the symptoms and management of agranulocytosis and should be given written guidance.
- Surgery for hyperparathyroidism is only required in a minority of patients.
- Hypoparathyroidism can occur after thyroid surgery. It is managed with vitamin D analogues and requires lifelong monitoring.

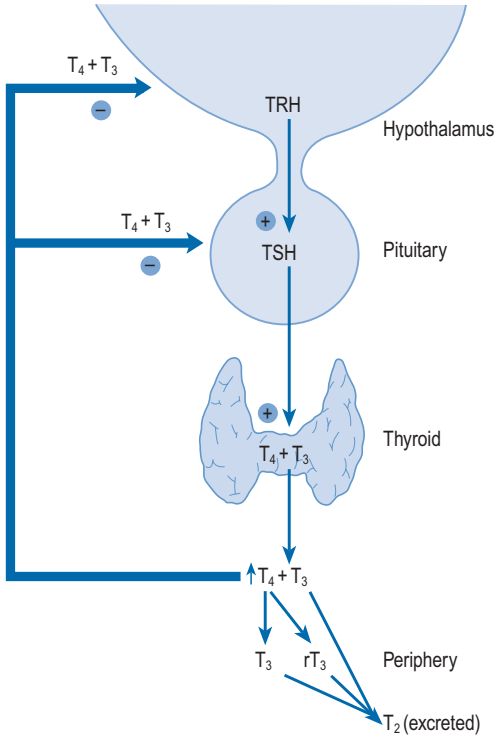


Fig. 43.1 Control of thyroid hormone secretion.

Thyroid physiology

The thyroid gland consists of two lobes and is situated in the lower neck. The gland synthesises, stores and releases two major metabolically active hormones: Tetra-iodothyronine (Thyroxine, T_4) and tri-iodothyronine (T_3). Regulation of hormone synthesis is by variable secretion of the glycoprotein hormone TSH from the anterior pituitary. In turn, TSH is regulated by hypothalamic secretion of the tripeptide thyrotrophin-releasing hormone (TRH) (Fig. 43.1). Low circulating levels of thyroid hormones initiate the release of TSH and probably also TRH. Rising levels of TSH promote increased iodide trapping by the gland and a subsequent increase in thyroid hormone synthesis. The increase in circulating hormone levels feeds back on the pituitary and hypothalamus, shutting off TRH, TSH and further hormone synthesis.

Both T_4 and T_3 are produced within the follicular cells in the thyroid. The stages in synthesis are shown in Fig. 43.2. In summary:

- Thyroglobulin and thyroid peroxidase (TPO) are synthesised by follicular cells.
- Hydrogen peroxide (H_2O_2) is synthesised at the luminal membrane.
- Dietary inorganic iodide is trapped from the circulation and transported to the follicular lumen where it is oxidised by H_2O_2.
- Iodine is then transferred onto the tyrosine residues in thyroglobulin by iodinase enzymes forming monoiodotyrosine (MIT) and di-iodotyrosine (DIT).
- Subsequently, the formation of T_4 occurs as a result of the coupling of two DIT residues and of T_3 by coupling a DIT and an MIT residue. The hormones are then stored within the gland until their release into the circulation.
- Finally, thyroglobulin is resorbed into the follicular cell, hydrolysed and its amino acids and remaining iodine re-used.

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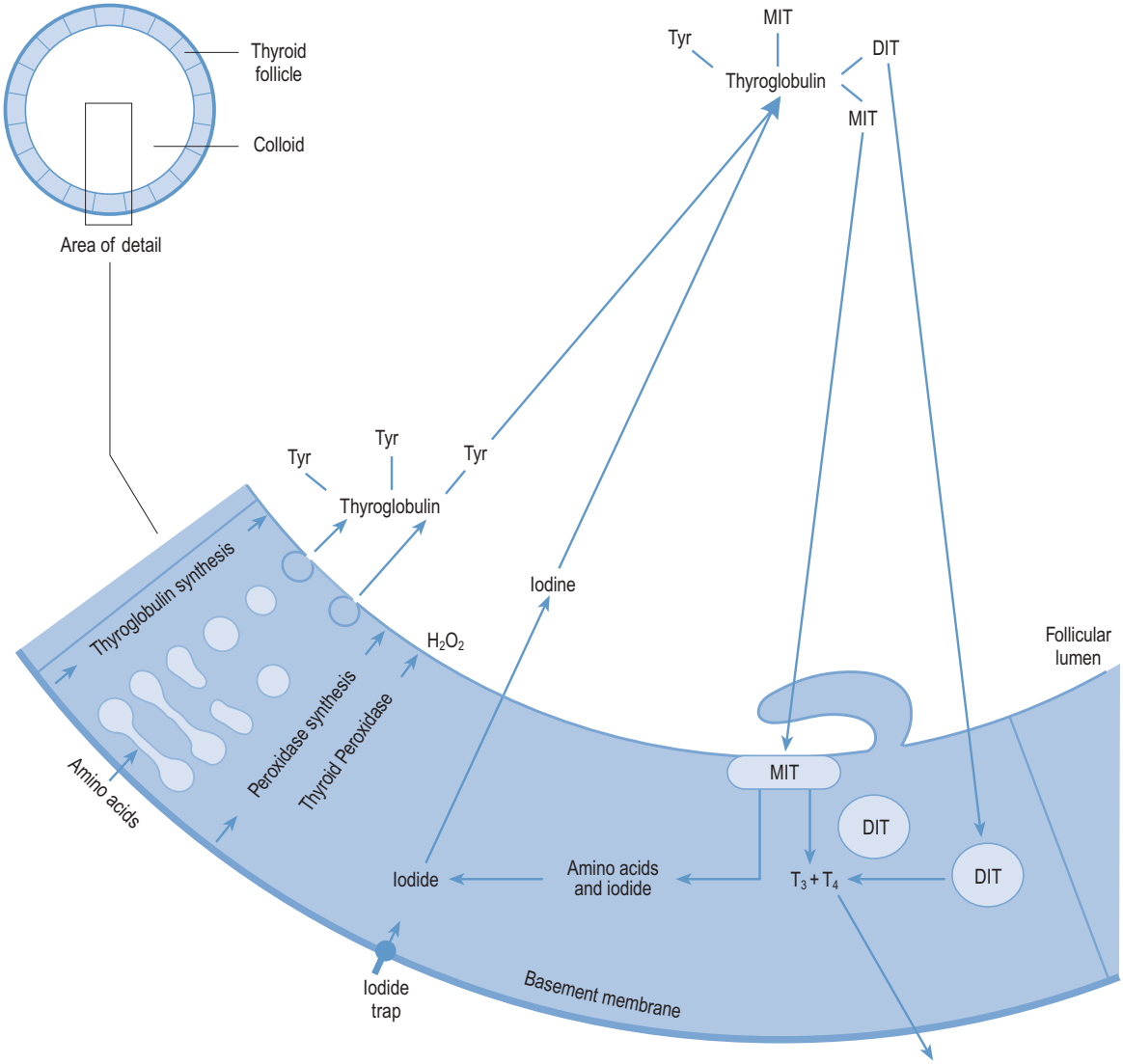


Fig. 43.2 Synthesis of thyroid hormones.

The ratio of T_4:T_3 secreted by the thyroid gland is approximately 10:1. Consequently, the gland secretes approximately 80–100 µcg of T_4 and 10 µcg of T_3 per day. However, only 10% of circulating T_3 is derived from direct thyroidal secretion, the remaining 90% being produced by peripheral conversion from T_4. T_4 can therefore be considered a prohormone that is converted in the peripheral tissues (liver, kidney and brain) either to the active hormone T_3 or to the biologically inactive reverse T_3 (rT_3). In the circulation, the hormones exist in both the active free and inactive protein-bound forms. T_4 is 99.98% bound, with only 0.02% circulating free. T_3 is slightly less protein bound (99.8%), resulting in a considerably higher circulating free fraction (0.2%). Details of protein binding are shown in Table 43.1.

The hormones are metabolised in the periphery (kidney, liver and heart) by deiodination. T_4 and T_3 are also eliminated by biliary secretion of their glucuronide and sulphate conjugates (15–20%). The half-life of T_4 in plasma is about 6–7 days and that of T_3 24–36 h in euthyroid adults. The apparent volume of distribution for T_4 is about 10 L and for T_3 about 40 L.

Table 43.1 Plasma protein binding of thyroid hormones

Carrier protein	Plasma concentration	Proportion of T_4 and T_3 bound (%)
Thyroid-binding globulin (TBG)	15 mg/L	75
Transthyretin (formerly thyroid-binding prealbumin)	250 mg/L	10
Albumin	40 g/L	15

Hypothyroidism

Hypothyroidism is the clinical state resulting from decreased production of thyroid hormones or very rarely from tissue resistance.

Epidemiology

Accurate assessment of the prevalence and incidence of hypothyroidism is difficult due to variation in definitions and population samples. The prevalence of previously undiagnosed, spontaneous, overt hypothyroidism has been estimated to be between 2 and 4 per 1000 of the total population worldwide. However, if all cases of previously diagnosed hypothyroidism and the effects of previous thyroid surgery and radioiodine treatment are included, this prevalence rises to approximately 10 per 1000. In the UK, primary hypothyroidism is common with a prevalence of 14/1000 women (but <1/1000 men). Despite these data, population screening for autoimmune hypothyroidism is thought to be probably not cost-effective unless incorporated into a screening programme for other conditions. Although the disease may occur at any age, most patients present between 30 and 60 years of age.

Aetiology

Primary hypothyroidism accounts for more than 95% of adult cases. It is usually due to a failure of the thyroid gland itself as a result of autoimmune destruction, or the effects of treatment of thyrotoxicosis. Hypothyroidism may be drug induced. Amiodarone and lithium cause hypothyroidism in around 10% of patients treated (see later). Secondary disease is due to hypopituitarism, and tertiary disease due to failure of the hypothalamus. Peripheral hypothyroidism is due to tissue insensitivity to the action of thyroid hormones. A more extensive classification is shown in Box 43.1.

Iodides may produce hypothyroidism in patients who are particularly sensitive to their ability to block the active transport pump of the thyroid gland. Iodine absorption from topical iodine-containing antiseptics has been shown to cause hypothyroidism in neonates. This is potentially very dangerous at a critical time of neurological development in the newborn infant. Transient hypothyroidism may be seen in 25% of iodine-exposed infants.

Box 43.1 Classification of hypothyroidism

Primary hypothyroidism
Congenital hypothyroidism
Agenesis
Inherited enzyme defects
Immune
Hashimoto's thyroiditis
Spontaneous hypothyroidism in Graves' disease
Postpartum hypothyroidism
Iatrogenic
Postoperative hypothyroidism
Hypothyroidism after radioactive iodine
External neck irradiation
Drugs – antithyroid thionamides, amiodarone, lithium, elemental iodide
Iodine deficiency
Subacute (viral)
Secondary/tertiary hypothyroidism
Hypopituitarism – any cause
Hypothalamic disease
Peripheral hypothyroidism
Insensitivity to thyroid hormones

Clinical manifestations

Hypothyroidism can affect multiple body systems, but symptoms are mainly non specific and gradual in onset (Box 43.2). Symptoms are frequently vague especially in the early stages. It is common for symptoms to be incorrectly attributed by patients and their relatives to increasing age. The reverse is also common in that patients who have read about, or have friends/family with, hypothyroidism will assume that it is responsible for symptoms of fatigue and weight gain. Thus, hypothyroidism is often confused with simple obesity and depression. Thyroid function tests give accurate diagnosis in all cases.

The most useful clinical signs are myotonic (slow-relaxing) tendon reflexes, bradycardia, hair loss and cool, dry skin. Effusions may occur into pericardial, pleural, peritoneal or joint spaces. Mild anaemia of a macrocytic type is quite common and responds to thyroxine replacement. Pernicious anaemia is a frequent concomitant finding in hypothyroidism. Other, organ-specific autoimmune diseases such as Addison's disease may be associated.

Myxoedema coma

Myxoedema coma is a rare but potentially fatal complication of severe, untreated hypothyroidism. Coma can be precipitated by hypothermia, stress, infection, trauma and certain

Box 43.2 Signs and symptoms of hypothyroidism

Skin and appendages	Dry, cool, flaking, thickened skin Reduced sweating Yellowish complexion. Puffy facies and eyes Sparse, coarse, dry hair Brittle nails
Neuromuscular system	Slow speech Poor memory and reduced cognitive function Somnolence Carpal tunnel syndrome Psychiatric disturbance Hearing loss Depression Muscle pain and weakness Delayed deep tendon reflexes
Metabolic abnormalities	Raised total and LDL cholesterol Macrocytic anaemia
Gastro-intestinal	Weight gain with decreased appetite Abdominal distension and ascites Constipation
Cardiovascular	Reduced cardiac output Bradycardia Cardiac enlargement

drugs, notably β-blockers and respiratory depressants, including anaesthetic agents, narcotics, phenothiazines and hypnotics. The condition is a medical emergency and should be treated rapidly and aggressively.

The term 'myxoedema' used to be synonymous with hypothyroidism. It is now reserved for advanced disease in which there is swelling of the skin and subcutaneous tissues.

Investigations

The laboratory investigation of hypothyroidism is extremely simple. Usually clinical assessment, combined with a single estimation of thyroid hormones and TSH, is sufficient to make the diagnosis. In primary disease, the levels of free T_4 and T_3 are low and the TSH level rises markedly. Some laboratories offer only TSH as a first-line test of thyroid function though this can result in delayed diagnosis of secondary or tertiary hypothyroidism, which should be suspected on the basis of a low free T_4 along with low TSH levels.

Elevation of the TSH level occurs early in the course of thyroid failure and may be present before overt clinical manifestations appear. It is important to appreciate that hypothyroidism is not one disease but a spectrum. Early hypothyroidism may be asymptomatic or the symptoms less obvious and non-specific, but a normal TSH with normal free T4 effectively excludes the diagnosis.

A chest radiograph may detect the presence of effusions, and an electrocardiogram (ECG) is useful, especially in patients with angina or coronary heart disease, in whom replacement therapy needs to be introduced gradually.

Testing thyroid function

As indicated earlier (and later in the section on thyrotoxicosis), a clinical assessment and measurement of free T_4 and TSH are usually all that are necessary to arrive at an accurate diagnosis of thyroid state. All modern TSH assays now employ double antibody immunometric techniques, which are robust and highly reliable. Moreover, these assays are now so sensitive that they are able to identify thyrotoxic patients with TSH levels below the normal euthyroid range. Commercial free T_4 and free T_3 assays, however, are all indirect methods and are subject to interference from drugs and other disease states. As such, both T_3 and T_4 can be decreased as a non-specific consequence of systemic illness ('sick euthyroid' syndrome) and depression along with a host of drugs (Surks and Sievert, 1995), which can interfere with thyroid hormone metabolism and free hormone assays (Table 43.2). Such patients require specialist assessment and collaboration with the local laboratory to rule out confounding disease and pituitary failure.

Table 43.2 Drug effects on thyroid function

	Clinical/biochemical effects
Decrease TSH secretion	
Dopamine Glucocorticoids Octreotide	Hypothyroidism (rarely clinically important)
Alter thyroid hormone secretion	
Iodide (amiodarone, contrast agents)	Both hyper- and hypothyroidism
Lithium	Hypothyroidism
Decrease T_4 absorption	
Colestyramine/colestipol Aluminium hydroxide Ferrous sulphate Calcium carbonate Multivitamins Sevelamer Protein pump inhibitors Sucralfate	Increased thyroxine dose requirement
Alter T_4 and T_3 metabolism	
Increased hepatic metabolism	
Phenobarbital Phenytoin Rifampicin Carbamazepine	Low T_4 and T_3 levels Normal or increased TSH
Reduce conversion of T_4 to T_3	
B-blockers Propylthiouracil Amiodarone Glucocorticoids	Lower T_3 levels Normal or increased TSH
Reduce T_4 and T_3 binding	
Furosemide Salicylates and NSAIDs Heparin	Increased measured free T_4 in some assays
Increase thyroglobulin levels	
Oestrogen and tamoxifen Opiates and methadone	Increased total T_4
Others	
Cytokines – interferon and interleukin 2	Thyroiditis. Can produce hypothyroidism and thyrotoxicosis

Treatment

The aims of treatment with thyroxine are to ensure that patients receive a dose that will restore well-being and that usually returns the TSH level to the lower end of the normal range (Vanderpump et al., 1996). All patients with symptomatic hypothyroidism require replacement therapy. T_4 is usually the treatment of choice except in myxoedema coma where T_3 may be used in the first instance. Before commencing T_4 replacement, the diagnosis of glucocorticoid deficiency must be excluded to prevent precipitation of a hypoadrenal crisis. If in doubt, hydrocortisone replacement should be given concomitantly until cortisol deficiency is excluded.

The initial dose of T_4 will depend on the patient's age, severity and duration of disease and the coexistence of cardiac disease. In young, healthy patients with disease of short duration, T_4 may be commenced in a dose of 50–100 μcg daily. As

the drug has a long half-life, it should be given once daily. The most convenient time is usually in the morning. After 6 weeks on the same dose (not a shorter interval as TSH takes this time to stabilise after a dose change), thyroid function tests should be checked. The TSH concentration is the best indicator of the thyroid state, and this should be used for further dosage adjustment. A raised TSH concentration indicates inadequate treatment, poor adherence or both. The majority of patients will be controlled with doses of 100–200 µcg daily, with few patients requiring more than 200 µcg. In adults, the median dose required to suppress TSH to normal is 125 µcg daily. In the majority of patients, once the appropriate dose has been established, it remains constant. During pregnancy, an increase in the dose of thyroxine by 25–50% is needed to maintain normal TSH levels.

Exacerbation of myocardial ischaemia, infarction and sudden death are all well-recognised complications of T_4 replacement therapy. Patients with coronary heart disease may be unable to tolerate full replacement doses because of palpitations, angina or heart failure. Elderly patients may have undiagnosed ischemic heart disease. In these two groups of patients, treatment should therefore be started with 25 µcg daily and increased slowly by 25 µcg every 4–6 weeks. During this time, the patient's clinical progress should be carefully monitored. In some patients, T_4 may be better tolerated if a β-blocker such as propranolol is given concomitantly. Some authorities recommend starting with 5 µcg of T_3, the rationale being that if adverse effects occur, these can be alleviated more rapidly with a dose reduction due to the shorter half-life of T_3.

It is important to avoid both under- and overtreatment. Hypothyroidism is very rarely life threatening, but adverse effects may result from prolonged overtreatment (which is indicated by a TSH level suppressed below the normal range). Though T_4 exerts an effect on many organs and tissues, it is the effect on bone and the heart that give the greatest cause for concern. There is evidence that bone density is reduced in patients taking excessive T_4 replacement therapy (Faber and Galloe, 1994; Uzzan et al., 1996), and that atrial fibrillation is more common if TSH is suppressed (Sawin et al., 1994). In order to minimise the risk of development of these complications, the dose of T_4 should be carefully tailored to the needs of each individual patient. Some patients will have undetectable serum TSH levels while taking thyroxine and may complain of recurrent fatigue if the dose is reduced to permit the TSH to rise. In these patients, it may be permissible to leave the dose unchanged if levels of free T_4 and T_3 are normal, after a discussion of the relative risks and benefits with the patient (Vanderpump et al., 1996).

Patient care

Hypothyroidism requires lifelong treatment with T_4. Patients on long-term drug therapy are recognised to have a low adherence with their medication regimen. Treatment with T_4 is often terminated because patients feel well and think that treatment is no longer required. Patients should understand the effects of drug holidays on their health and thyroid function tests and should know that a normal TSH indicates adequate dosage. Written advice should be provided and monitoring of dosage should continue annually. There are a series of excellent patient information leaflets available on the British Thyroid Association website at www.british-thyroid-association.org.

Despite adequate counselling, some patients persistently forget to take their tablets reliably, leading to variable thyroid state and wildly fluctuating test results. Other patients lack capacity to self-medicate reliably. There is evidence to show that weekly dosing with T_4 is a safe and acceptable way to manage this type of patient, in whom family members or community staff can supervise treatment (Grebe et al., 1997; Rangan et al., 2007). There are no guidelines yet published, but in practice, patients are normally started on 500–700 µcg T_4 weekly. Dose changes are made in exactly the same way by assessing TSH levels after 6 weeks of stable dosing.

Rarely, patients are seen in whom TSH levels fluctuate or remain elevated despite high doses of thyroxine and in whom adherence seems to be very good. There are a number of possible causes for this, including malabsorption of thyroxine which can be due to coeliac or inflammatory bowel disease or a number of commonly prescribed drugs (Table 43.2). Such patients will need a careful sequential assessment by an endocrine service (Morris, 2009).

Prevention

At present, nothing can be done to prevent autoimmune thyroid failure from developing; however, much can be done to ensure early detection and treatment. Careful follow-up of patients who have undergone radioiodine treatment, subtotal thyroidectomy or completed a course of treatment for thyrotoxicosis is essential along with monitoring of those prescribed amiodarone and lithium. An increase in TSH with normal concentrations of T_3 and T_4 will indicate the onset of hypothyroidism before the patient becomes symptomatic. Box 43.3 shows the prevalence of hypothyroidism after treatment for thyrotoxicosis.

Box 43.3 Prevalence of thyroid disturbance after treatment for thyrotoxicosis

Thyroidectomy
6–75% develop hypothyroidism over their lifetime, dependent on the amount of remnant tissue.
Risk highest during first year after surgery

Antithyroid drugs (>6 month course)
43% relapse with thyrotoxicosis in the first year
13–21% relapse with thyrotoxicosis in the next 4 years

^{131}I therapy
24–90% develop hypothyroidism over their lifetime, depending on dose given

Hyperthyroidism/thyrotoxicosis

Hyperthyroidism is defined as the production by the thyroid gland of excessive amounts of thyroid hormones. Thyrotoxicosis refers to the clinical syndrome associated with prolonged exposure to elevated levels of thyroid hormone. This distinction is important when evaluating thyroid function tests (Table 43.3).

Epidemiology

Hyperthyroidism is a common condition. It has been estimated that there are 4.7/1000 women with active disease. When previously treated cases were included, the population prevalence rose to 20/1000 in women. As for hypothyroidism, it is much less common in men who have a lifetime prevalence of around 2/1000 (Tunbridge et al., 1977).

Aetiology

Hyperthyroidism is a disorder of various aetiologies. In clinical terms, thyrotoxicosis is the result of persistently elevated levels of thyroid hormones.

Graves' disease

Graves' disease is the commonest cause of thyrotoxicosis. It is an autoimmune condition and results from production of an abnormal IgG immunoglobulin which is able to occupy the TSH receptor on the thyroid follicular cell. Here, it mimics the effect of TSH, causing cell division and stimulating thyroid hormone secretion. These stimulatory imunoglobulins are known as thyroid receptor antibodies (TRABs). Very rarely, the TRABs are inhibitory to the TSH receptor, resulting in hypothyroidism.

Ninety per cent of patients with Graves' disease are young women often with a family history of the condition. In addition to the effects of thyrotoxicosis, around 30% of patients develop additional features including a congestive ophthalmopathy which is thought to result from antibody-mediated inflammation of orbital contents. Pretibial myxoedema, gynaecomastia and thyroid acropachy are rare manifestations.

In pregnancy, the maternal TRABs can pass across the placenta to the fetus resulting in transient neonatal thyrotoxicosis.

Nodular disease

Toxic multinodular goitre is also common but more often affects older women in whom an euthyroid nodular goitre may have been present for many years. Individual nodules become autonomous, producing T_3 and/or T_4. Clinically, the thyrotoxicosis is generally less severe and more gradual in onset. Often, only T_3 levels are elevated, though the TSH will be suppressed in all cases. Thyrotoxicosis may also be caused by single autonomous thyroid adenomas. These are benign well-differentiated tumours that secrete excessive amounts of thyroid hormones.

Table 43.3 Aetiology of hyperthyroidism

	Condition	Frequency	Clinical features	I^{131} uptake
Thyrotoxicosis (increased hormone synthesis)				
	Graves' disease	70%	Antibody mediated (TRABs) 90% are young women Diffuse goitre Ophthalmopathy (30%) Pretibial myxoedema Acropachy Transmissible to neonate	Increased
	Multinodular goitre	20%	Benign autonomous nodules Often secrete T_3 Older women Always relapse after withdrawal of thionamides	Increased
	Toxic single adenoma	5%		Increased
	Iodine induced	<1%	Increased urine iodine	Variable
	HCG induced	Rare	Molar pregnancy or choriocarcinoma	Increased
	TSH dependent	Rare	Pituitary tumour	Increased
Thyroiditis (thyroid destruction and leakage of stored thyroid hormones)				
	Acute	2%	Probably viral Neck pain – often severe	Absent
	Silent	2%	Viral Autoimmune	Absent
	Amiodarone induced	<1%	Increased urine iodine	Absent

TRABs, thyroid receptor antibodies.

Thyroiditis

If the thyroid is inflamed by viral or rapid autoimmune attack, the resulting follicular cell death will result in the release of pre-formed thyroid hormones. This usually presents as a painful mildly enlarged and tender thyroid. There is a brief period of hyperthyroidism before thyroid hormone levels fall to subnormal. Most often, this period of hyperthyroidism does not lead to clinically apparent thyrotoxicosis and in any event is brief, but it is common for these patients to be prescribed thionamides which compound the ensuing hypothyroidism. It is therefore necessary to be aware of these conditions. Neck pain with disturbed TFTs should prompt referral for specialist assessment which will usually include a request for an iodine uptake scan. Iodine uptake is absent in hyperthyroidism associated with thyroiditis.

Clinical manifestations

Thyrotoxicosis is characterised by increases in metabolic rate and activity of many systems due to excessive circulating quantities of thyroid hormones. There is a wide spectrum of clinical disturbances. The signs and symptoms reflect increased adrenergic activity, especially in the cardiovascular and neurological systems (Box 43.4). Not all manifestations will be seen in every patient. Additional clinical features will depend on the underlying cause of the thyrotoxicosis (Table 43.3).

The clinical features of thyrotoxicosis in the elderly may not be so obvious. Signs and symptoms of cardiovascular disturbance tend to predominate, atrial fibrillation is frequent and the patient may develop congestive cardiac failure. Unexplained heart failure after middle age should always arouse suspicion of thyrotoxicosis.

The extrathyroidal manifestations of Graves' disease deserve separate mention. Most frequent is ophthalmopathy due to inflammation and expansion of the contents of the orbit. The eye is pushed forward (proposed) such that white sclera appears between the iris and the lower lid. Congestive changes develop including peri-orbital oedema, conjunctival swelling and redness. The extraocular muscles are swollen and become tethered leading to failure of movement of the globe of the eye and thus diplopia. Severe disease causes pressure in the orbit, which can compress the optic nerve leading to blindness. The cutaneous features of Graves' disease include thickening of the pretibial skin (myxoedema), onycholysis (separation of the nail from the nail bed) and acropachy (similar to finger clubbing).

Box 43.4 Signs and symptoms of thyrotoxicosis

Skin and appendages	Warm, moist skin Thinning or loss of hair Increased sweating Heat intolerance
Nervous system	Insomnia Irritability, nervousness Lid retraction – staring eyes Symptoms of an anxiety state Psychosis
Musculoskeletal	Fine motor tremor Proximal muscle weakness Rapid deep tendon reflexes Osteoporosis
Gastro-intestinal	Weight loss despite increased appetite Thirst Diarrhoea
Cardiovascular	Palpitations, tachycardia Shortness of breath on exertion Atrial fibrillation Congestive cardiac failure Worsening angina

Investigations

In those with suspected thyrotoxicosis, it is good practice to document the diagnosis with two sets of thyroid function tests. If the diagnosis is in doubt, treatment should be withheld because unless severe, thyrotoxicosis can usually be safely observed whilst awaiting the results of investigations. Plasma free T_4 (and/or T_3) levels are elevated. The TSH level is suppressed to subnormal levels in all causes of thyrotoxicosis, except the exceptionally rare cases of TSH secreting pituitary adenomas.

In the overwhelming majority of patients, the combination of the clinical findings and simple investigations is sufficient to make a firm diagnosis. Radioactive iodine uptake scans will differentiate those patients with thyroiditis. Measurement of TRABs will identify Graves' disease patients. If the diagnosis is still equivocal, the clinical findings should be reassessed and particular attention paid to the patient's drug history. There are a number of drugs that may modify the clinical features or interfere with the tests.

Treatment

A number of factors need to be considered when choosing the most appropriate form of therapy for an individual patient (Table 43.4). There are usually a number of therapeutic options available, and the patient should be involved in the deciding on treatment. The decision may also be influenced by physician preference, which in turn can depend on the facilities available. Three forms of therapy are available, including anti-thyroid drugs, surgery and radioactive iodine. There is no general agreement as to the specific indications for each form of therapy, and none of them is ideal, all being associated with both short- and long-term sequelae. Neither surgery nor radioactive iodine should be given until the patient has been rendered euthyroid due to the risk of inducing a thyroid crisis.

In children, surgery may be difficult and the complication rate is higher. Also, radioiodine has been avoided due to concern about the potential development of thyroid malignancy, though there are no data which suggest this to be a

Table 43.4 Treatments available for thyrotoxicosis

	Adverse effects (%)	Contraindications	Cautions
Thionamides Carbimazole Propylthiouracil	Rash/arthropathy (5%) Agranulocytosis (0.3%) Hepatitis (rare)	Previous severe allergy Cross reactivity in 10%	Pregnancy – PTU preferred. Do not use block/replace regimens
Radioiodine	Hypothyroidism requiring lifelong T_4	Pregnancy	Ensure euthyroid first Ophthalmopathy may deteriorate
Surgery	Hospital stay Neck scar Surgical/anaesthetic risk 10–75% require T_4		Ensure euthyroid first Ophthalmopathy may deteriorate

problem. In pregnancy, radioiodine is not used due to the likelihood of producing a hypothyroid neonate. Thyroid surgery during pregnancy should be deferred until the second trimester if possible and most patients can be controlled with drugs. Thionamide doses should be kept as low as possible, especially in the last 2 months of pregnancy, as excessive treatment may produce goitre in the fetus. Aplasia cutis is said to occur after carbimazole therapy, so propylthiouracil (PTU) is usually used in pregnancy. Pregnant patients with thyrotoxicosis should be under the care of a specialist endocrine unit.

Immediate treatment of thyrotoxicosis

Patients need to have their symptoms addressed and their thyrotoxicosis controlled. β-Blockers in standard antihypertensive doses are effective within a matter of hours and should be offered to all non-asthmatics with severe thyrotoxicosis. Carbimazole (40 mg once a day) or PTU (150 mg twice daily) will render most patients euthyroid within 6 weeks. Adjunctive treatment of cardiac disease and anxiety/sleeplessness may be required.

Graves' disease

A proportion (40–50%) of patients with Graves' disease will achieve a long-lasting remission after a period of euthyroidism on thionamides. The optimal duration of anti-thyroid treatment is unknown and remains a controversial issue (Maugendre et al., 1999), but in most units, the length of the treatment course has fallen to between 6 and 12 months. It is not appropriate to discuss complex treatment decisions with a thyrotoxic patient, so most are well into this period when discussions of their options occur. Remission of Graves' disease is much less likely in those with very large goitres, those who require high-dose thionamide treatment to maintain euthyroidism, those with high TRAB titres and patients who have relapsed once after a course of drug treatment. Such patients should therefore be rendered euthyroid and then have a discussion about either surgical or radioiodine thyroid ablation.

Nodular thyroid disease

As the nodules function autonomously and thyrotoxicosis will always recur when thionamides are stopped, there is no value in attempting to achieve a remission of nodular thyroid disease using prolonged medical treatment. Patients should be rendered euthyroid with drugs and then have a discussion about ablative therapy.

Anti-thyroid drugs

The thionamides, PTU, thiamazole (methimazole) and its precursor carbimazole are equally effective pharmacological therapies for thyrotoxicosis. In the UK, carbimazole is usually used. These drugs prevent thyroid hormone synthesis by inhibiting the oxidative binding of iodide and its coupling to tyrosine residues. PTU, but not carbimazole, inhibits the peripheral deiodination of T_4 to T_3. Thionamides may also have an immunosuppressive action.

Adverse effects. The most common adverse effect of anti-thyroid treatment is rash and arthropathy (5%) and less commonly agranulocytosis, hepatitis, aplastic anaemia and lupus-like syndromes (Table 43.5). Overall, serious effects such as these occur in approximately 0.3% of patients treated. These side effects usually occur during the first 6 weeks of treatment, but this is not invariable. Cross-sensitivity between carbimazole and PTU is around 10%, and the patient can often be safely changed to the alternative agent if an adverse event occurs.

Regular monitoring of white cell counts has been advocated, but is not warranted. Agranulocytosis is a rare event, and even if it does occur, it happens rapidly such that routine monitoring of white cell counts may miss it. At the time of prescription, all patients should be counselled about the possible implication of sore throat, mouth ulcers and pyrexia, and instructed to seek an urgent (within hours) full blood count. This verbal information should be backed up by written advice which should specify where the patient should go for the blood test. An abnormal white cell count should prompt urgent admission under a specialist endocrine team.

Table 43.5 Adverse effects of thionamides

	Adverse effect	Comments
Skin	Pruritic, maculopapular rash	Most common in first 6 weeks May disappear spontaneously with continued treatment Can be treated with an antihistamine Change to alternative agent Occurs in 5% of patients
	Urticarial rash with systemic symptoms, that is fever, arthralgia	Discontinue drug Alternative treatment required
Haematological	Agranulocytosis	Most common in first 6 weeks Incidence increases with age Discontinue drug Reversible Consider alternative treatment Occurs in 0.3% of patients
	Leucopoenia	Transient Continue treatment Does not predispose to agranulocytosis
Other	Hepatitis Vasculitis Hypoprothrombinaemia Aplastic anaemia Thrombocytopenia	Rare Discontinue drug

Treatment regimen

Carbimazole is usually given initially at a dose up to 40–60 mg daily, depending on the severity of the condition. It can be given as a single daily dose in multiples of 20 mg tablets to aid adherence. Although the plasma half-life is short (4–6 h), the biological effect lasts longer (up to 40 h). T_4 concentrations are checked at 6-week intervals until the patient is clinically euthyroid and the T_4 and T_3 levels are normalised. (TSH remains suppressed for at least 4 weeks after resolution of significant thyrotoxicosis, so TSH levels are unhelpful in the early stages of treatment.)

At this point, a decision is made about ongoing treatment. It is simplest to continue a high dose of carbimazole to suppress endogenous thyroid hormone production and to give a standard replacement dose of thyroxine to maintain euthyroidism, the 'block and replacement' regimen. This combination results in a steadier thyroid state, reduces the need for blood monitoring and requires fewer hospital attendances. Since adverse drug effects are allergic and not dose related, it is no more risky than tailored dose regimens.

Pregnancy is a specific situation, however, in which tailored dose PTU should be used. Both the immunoglobulins which cause Graves' disease and thionamide drugs cross the placenta and will affect the fetal thyroid, but maternal thyroxine is not able to reach the fetus. Thus, the lowest possible dose of PTU (preferred to carbimazole in pregnancy) should be used and the fetus closely monitored for heart rate and growth. Breastfeeding is considered to be safe when mothers are taking thionamides.

Patient counselling

Patients should be advised of the importance of regular clinic attendance. This is necessary to monitor both therapeutic outcome and the development of adverse effects. The development of skin rashes, mouth ulcers or a sore throat should be reported by the patient, immediately investigated and a full blood count performed (see Box 43.5). It may be dangerous to treat these symptoms with over-the-counter medication before carrying out further investigations.

It is important for the patient to understand the difference between specific anti-thyroid therapy and symptomatic treatment. The patient should also be advised about the timing of doses to aid adherence. Following completion of a course of treatment, the patient should understand relapse may occur, and medical help should be sought if the initial symptoms recur.

Thyroid ablative therapy

Thyroid ablation is required for all patients with toxic multinodular goitres, those who have relapsed or are likely to relapse after drug therapy for Graves' disease and those who are allergic to thionamides. Thyroid ablation can be achieved by radioiodine or surgery.

Radioactive iodine. Radioiodine therapy is extremely easy to administer by mouth and is very effective for a large majority of patients. It is contraindicated in pregnancy and breastfeeding and is usually avoided in children. It is known to make ophthalmopathy worse in some patients with Graves' disease, but giving prednisolone 0.5 mg/kg for 3 weeks and commencing thyroxine replacement early (3 weeks after radioiodine) can mitigate this. Despite public concern in relation to radioactivity, accumulated experience over more than 60 years has not demonstrated any discernible risk of genetic, leukaemic or lymphoma risk (Vanderpump et al., 1996).

Box 43.5 Counselling points for patients on anti-thyroid drugs

1. Carbimazole can be given as a single daily dose.
2. Identify anticipated duration of treatment.
3. Explain block and replacement regimens.
4. Explain use of adjuvant therapy, for example, β-blockers.
5. Encourage reporting of skin rashes, sore throat or mouth ulcers. Provide written guidance.
6. Ensure the patient understands the need for regular review.
7. Outline management of relapse.

The commonest complication is the development of hypothyroidism. Doses sufficient to cause thyrotoxicosis to remit will result in virtually 100% of patients given radioiodine for Graves' disease becoming hypothyroid and around 50% of those treated for multinodular disease. Patients should be counselled to expect to require lifelong thyroxine treatment after radioiodine therapy.

Anti-thyroid drugs must be withdrawn before radioiodine is given and should not be restarted for at least 3 days afterwards (otherwise, the isotope will not be trapped by the thyroid). The author conventionally recommends they be stopped 7 days before radioiodine. Since the ablative effect of radioiodine usually commences within 2–3 months, many patients with mild or moderate disease will not need to restart their drug treatments, though close patient monitoring is required. Patients with severe thyrotoxicosis should restart their anti-thyroid drugs on day 3. Treatment is then withdrawn periodically to assess the effects of the radioiodine.

The patient receiving radioiodine treatment is effectively radioactive for 6 weeks without ill effect. Since the patients are not at risk from this radioactivity, it seems inherently unlikely that the public faces any risk at all to health. Nevertheless, there are regulations governing exposure to radiation, which must be followed. After a standard 555-MBq dose, a patient must for 14 days avoid close continuous contact (2 m) with other persons for periods of more than 1 h, undertake to be careful in disposing of urine, and must not work. For 24 days, they must avoid close contact with children and pregnant women. In practice, it is these regulations and the concerns they engender in the patient that result in a proportion of patients preferring a surgical approach.

Surgery

Surgery is required for those patients with very large goitres, patients who cannot be persuaded of the safety of radioiodine and those who have reacted adversely to both thionamides in pregnancy. The hyperthyroid patient to be treated surgically should first be rendered biochemically euthyroid whenever possible, but occasionally surgery needs to be performed as a semi-urgent procedure. This may require urgent patient preparation with a combination of anti-thyroid drugs and β-blockers, and iodide given as Lugols solution. Iodide exerts a (usually) transient inhibitory effect on the ability of the gland to trap iodide, and it may also reduce the vascularity of the gland. In doses of 800–1200 mg/day, lithium is an effective anti-thyroid drug for patients who have reacted to thionamides. Lithium levels should be monitored to minimise toxicity. β-Blockers should be introduced and the dose titrated to reduce the pulse rate to below 80 beats/min. They are usually continued for 1 week postoperatively. It is imperative that treatment is given right up to the time of operation and the operation deferred if the pulse rate is not adequately controlled. Inadequate pre-treatment can result in the occurrence of thyroid crisis.

Complications of surgery include the generic ones of anaesthetic risk, bleeding, thromboembolic disease and infection. Specific risks of thyroid surgery include damage to recurrent laryngeal nerves (which may be particularly important to actors, singers and teachers) and hypoparathyroidism as a result of interference of the blood supply to the parathyroids or their inadvertent removal during surgery. If this occurs, tetany will begin within 48 h of the operation, and treatment should be initiated with intravenous calcium gluconate. All patients who have undergone partial thyroidectomy should have serum calcium estimation 3 months after operation since the development of hypoparathyroidism can be delayed. Later complications of thyroidectomy include hypothyroidism and recurrent thyrotoxicosis.

Treatment of complications

Ophthalmopathy

In most patients with Graves' disease, no specific treatment is required for the eyes. The commonest complaint is of 'grittiness', which can be treated with hypromellose eye drops or gel. If lid retraction is severe, inadequate lid closure can result in early morning soreness. This can be alleviated by the short-term use of 5% guanethidine eye drops instilled each night and morning. The eyes should be monitored for any signs of infection, and treated appropriately.

Fortunately, severe eye involvement occurs in less than 2% of patients with Graves' disease. Progressive ophthalmopathy producing severe complications from proptosis, diplopia or visual failure should be treated with high-dose steroid therapy (prednisolone, 60 mg daily) until symptoms resolve. Failure to respond is an indication for orbital irradiation or surgical decompression, but such patients should be under the care of a highly specialised ophthalmic surgeon.

Treatment of localised myxoedema

Myxoedema is usually localised to small areas and is asymptomatic. More extensive disease causes difficulty in walking and considerable discomfort. Probably the most effective therapy is the nightly topical application of steroid creams, such as betamethasone, under occlusive polythene dressings.

Thyroid crisis

This condition can develop in any patient with significant untreated thyrotoxicosis but is most common in those with severe Graves' disease. It is precipitated in such patients by infection, injury, trauma, anesthetics, surgery and radioiodine. There is rapidly progressive tachycardia, muscle weakness (including cardiomyopathy) hyperthermia, sweating and vomiting compounding hypotension with ensuing circulatory collapse. In addition, patients are extremely anxious and often psychotic. It should be managed as a medical emergency in a high-care area. In addition to supportive measures, specific anti-thyroid therapy is required along with drugs, which inhibit deiodination of T_4 to T_3. PTU (inhibits deiodinase) is given orally (or via NG tube) in high dose along with Lugols iodine. Glucocorticoids should be given i.v. as they also inhibit deiodinase. Effective β-blockade is required by i.v. infusion (propranolol preferred as it also inhibits deiodinase).

Drugs and the thyroid

From the previous pages, it will be evident that many commonly used drugs can affect the thyroid. This section draws together the most frequently encountered problems. In clinical practice, drug effects and interactions produce thyrotoxicosis, hypothyroidism or disturb thyroid function tests. It is worth specifically noting amiodarone, which contains large quantities of iodide which is released into the circulation during drug metabolism. The effects of amiodarone on the thyroid are extensive and complex.

Drugs and thyrotoxicosis

Table 43.2 indicates drug treatments associated with thyrotoxicosis. Amiodarone-induced thyrotoxicosis (AIT) is caused by two entirely different mechanisms. Type 1 AIT is similar to iodide-induced thyrotoxicosis and results from activation of nodular disease or of latent Graves' disease in patients with thyroid autoimmunity. In this condition, the thyroid is actively synthesising hormone and treatment is with thionamides. Type 2 AIT has features similar to thyroiditis with leakage of pre-formed thyroid hormone, low uptake of radiolabel on scanning and is treated with glucocorticoids. AIT is an extremely challenging condition to manage for multiple reasons. These include difficulty in discrimination between type 1 and type 2 disease, each of which have different treatments, and the facts that most patients are taking amiodarone for serious cardiac dysrhythmias and amiodarone has a very long tissue half-life. These patients should be under the care of a specialist endocrinology team.

A recent observation has been the increased frequency of Graves' disease in patients undergoing bone marrow transplantation, after administration of alemtuzumab (CAMPATH, a monoclonal antibody to CD52 cells), or alpha-interferon for multiple sclerosis and during Highly Active Anti-Retroviral Treatment (HAART) of HIV infection. It is thought that these cases all have immunological reconstitution as an underlying factor in their aetiology (Weetman, 2009).

Drugs and hypothyroidism

Amiodarone is frequently associated with the development of hypothyroidism, particularly in those patients with positive TPO antibodies, indicative of latent Hashimoto's disease. Such patients seem particularly sensitive to the high levels of iodine liberated by drug metabolism, and it is thought that hypothyroidism occurs because of a failure of the patient's thyroid to escape from the suppressive effect of iodine on thyroxine synthesis (the Wolff-Chaikoff effect). If amiodarone can be withdrawn, hypothyroidism will resolve over a period of months. More often, however, amiodarone is continued and thyroxine treatment is required.

Lithium inhibits T_4 and T_3 release from the thyroid (making it a useful adjunctive treatment for thyrotoxicosis in patients who react to thionamides) and causes a goitre in 40% of patients and hypothyroidism in 20%, again more commonly in those with positive TPO antibodies. Like amiodarone, lithium is usually continued and these patients are treated with thyroxine. Drug-related interference with absorption of thyroxine is one of the causes of hypothyroidism in patients treated with thyroxine. Table 43.2 indicates the agents which may be implicated.

Calcium and parathyroid hormone

Physiology

Most individuals possess four parathyroid glands situated posterior to the upper and lower lobes of the thyroid. These glands secrete parathyroid hormone (PTH). Calcium is approximately 50% ionically bound to albumin, and it is the unbound ionised plasma calcium levels which regulate the secretion of PTH, increased calcium concentration suppressing secretion and low levels stimulating it. PTH is an 84-amino acid straight-chain polypeptide which acts on hormone-specific receptors on target tissue cells. PTH acts on the renal tubular transport of calcium and phosphate and also stimulates the renal synthesis of 1,25-dihydroxycolecalciferol.

PTH and vitamin D act to maintain plasma calcium levels within the normal range. PTH increases distal tubular reabsorption of calcium and decreases proximal and distal tubular reabsorption of phosphate. The effects of PTH on bone are complex. The two major cell types in bone are osteoblasts and osteoclasts. Osteoblasts are responsible for the synthesis of extracellular bone matrix and priming of its subsequent mineralisation. Osteoclasts decalcify and digest the protein matrix of bone, liberating calcium. PTH stimulates osteoclast-mediated bone resorption but, in addition, has an anabolic effect on bone, with an increase in osteoblast number and function.

Hypoparathyroidism/hypocalcaemia

Hypoparathyroidism is the clinical state which may arise either from failure of the parathyroid glands to secrete PTH or from failure of its action at the tissue level.

Aetiology

Hypoparathyroidism most commonly occurs as a result of surgery for thyroid disease or after neck exploration and resection of adenoma causing hyperparathyroidism. In experienced hands, the incidence of permanent hypoparathyroidism is less than 1% for all thyroid and parathyroid surgery. Other causes include autoimmune parathyroid destruction either as an isolated idiopathic disorder or as part of a multiple endocrine deficiency characterised by hyposecretion of several endocrine glands. Transient hypoparathyroidism with symptomatic hypocalcaemia can occur in neonates. The condition pseudohypoparathyroidism occurs in patients with defects of the PTH receptor such that though PTH levels are normal (or raised), calcium is low. Increasingly, reports are identifying acute symptomatic hypocalcaemia and hypomagnesaemia complicating the use of omeprazole and other protein pump

inhibitors. These patients are severely magnesium depleted and have an acquired hypoparathyroidism which is reversible on stopping the offending drug (Cundy and Dissanayake, 2008).

Clinical manifestations

Most of the clinical features of hypoparathyroidism are due to hypocalcaemia. The decrease in ionised plasma calcium levels leads to increased neuromuscular excitability. The major signs and symptoms are shown in Box 43.6.

Investigations

Hypocalcaemia associated with undetectable or low plasma PTH levels is consistent with hypoparathyroidism. Total plasma calcium levels should always be corrected for any abnormality in the plasma albumin concentration using the following equation.

$$\text{Corrected calcium} = \text{measured calcium} + \{0.02 \times (40 - \text{plasma albumin})\}$$

Hyperphosphataemia is often present. It should be noted that there are many other causes of hypocalcaemia (Box 43.7). Pseudohypoparathyroidism is easily distinguished as it is associated with excessive PTH secretion and reduced target organ responsiveness. Drugs that may produce hypocalcaemia include calcitonin, plicamycin (formerly mithramycin), phosphate, bisphosphonates, phenytoin, phenobarbital, colestyramine, cisplatin, 5-FU and high-dose i.v. citrate or lactate.

Treatment

Severe, acute hypocalcaemia with tetany should be treated with intravenous calcium gluconate. Initially, 10 mL of 10% calcium gluconate is given by slow intravenous injection, preferably with ECG monitoring. If the patient can swallow, oral therapy should then be commenced. If further parenteral therapy is required, 20 mL of 10% injection should be added to each 500 mL of intravenous fluid and given over 6 h. The plasma magnesium level should always be measured in patients with hypocalcaemia, and if low, magnesium therapy instituted.

For chronic treatment, PTH therapy is not currently a practical option as the hormone has to be administered parenterally, and the current high cost is prohibitive. Maintenance treatment for hypoparathyroidism is easily achieved with a vitamin D preparation to increase intestinal calcium absorption, often in conjunction with calcium supplementation. Details of the preparations available are given in Table 43.6. Ergocalciferol (vitamin D_2) is difficult to use and is not recommended. It has a long pharmacological and biological half-life, takes 4–8 weeks to restore normocalcaemia and its effects can persist for up to 4 months following withdrawal. In contrast, calcitriol and its synthetic analogue alfacalcidol are much easier to use. Alfacalcidol restores normocalcaemia within 1 week and its effects only persist for 1 week following withdrawal, permitting greater flexibility in dosage manipulation. The usual daily dose is 0.5–2 μcg. Patients need close monitoring initially until stable normocalcaemia is achieved and thereafter at a minimum of 6-month intervals indefinitely.

Box 43.6 Signs and symptoms of hypocalcaemia

- Numbness and tingling in the extremities and around the mouth
- Muscle spasm (tetany)
- Epilepsy
- Irritability
- Cataracts (prolonged hypocalcaemia)
- Chvostek's sign (facial spasm on tapping the 7th cranial nerve)
- Trousseau's sign (spasm of hand when blood pressure cuff inflated above systolic pressure)

Box 43.7 Causes of hypocalcaemia

- Hypoparathyroidism
- Pseudohypoparathyroidism
- Vitamin D deficiency/malabsorption/insensitivity
- Acute and chronic renal failure
- Chronic alcoholism
- Hypomagnesaemia
- Drug induced (protein pump inhibitors)
- Acute pancreatitis

Hyperparathyroidism

Hyperparathyroidism occurs when there is increased production of PTH by the parathyroid gland. Primary hyperparathyroidism causes hypercalcaemia. Secondary hyperparathyroidism reflects a physiological response to hypocalcaemia or hyperphosphataemia.

Epidemiology

Recent studies in the USA and Europe indicate an incidence rate for primary hyperparathyroidism of 25 cases per 100,000 of the population per year. The incidence is two to three times higher in women than in men, and the disease most commonly presents between the third and fifth decades.

Aetiology

Primary hyperparathyroidism is due to the development of either single parathyroid adenomas or rarely (<5%) hyperplasia of all four glands. It may occur as part of the dominantly inherited multiple endocrine neoplasia (MEN) syndromes.

There are several conditions associated with secondary hyperparathyroidism, including chronic renal failure and vitamin D deficiency. Chronic renal failure is the commonest cause. In the early stages of the disease, a rise in the plasma phosphate concentration causes stimulation of PTH release and, in more advanced renal impairment, reduced 1 α-hydroxylation of vitamin D results in reduced intestinal calcium absorption, hypocalcaemia and further stimulation

Table 43.6 Vitamin D preparations

Drug	Preparations	Activity
Ergocalciferol (calciferol, vitamin D_2)	Calciferol injection 7.5 mg (300,000 units/mL) Calciferol tablets 250 µcg (10,000 units) and 1.25 mg (50,000 units) Calcium and ergocalciferol tablets (2.4 mmol of calcium + 400 units of ergocalciferol)	Requires renal and hepatic activation
Colecalciferol (vitamin D_3)	A range of preparations containing calcium (500–600 mg) and colecalciferol (200–440 units)	Requires renal and hepatic activation
Alfacalcidol (1 α-hydroxycolecalciferol)	Alfacalcidol capsules, 250 ng, 500 ng and 1 µcg Alfacalcidol injection, 2 µcg/mL	Requires hepatic activation
Calcitriol (1,25-dihydroxycholecalciferol)	Calcitriol capsules, 250 ng and 500 ng Calcitriol injection, 1 µcg/mL	Active
Dihydrotachysterol	Dihydrotachysterol oral solution, 250 mg/ml	Requires hepatic activation

of the parathyroid glands. Tertiary hyperparathyroidism occurs in a minority of patients with end-stage renal failure when hyperplastic parathyroid glands become autonomous and secrete PTH in levels that raise calcium levels above normal.

Clinical manifestations

The clinical features of primary hyperparathyroidism are shown in Box 43.8. These are related to the effects of hypercalcaemia itself, plus the effects of mobilisation of calcium from the skeleton and excretion in the urine. With increasingly early recognition of the biochemical abnormalities of primary hyperparathyroidism largely due to automated measurement of plasma calcium, most patients are identified at an early stage with mild or asymptomatic disease. The classical presenting features of bone disease and renal stones are now relatively uncommon. Although radiological evidence of bone disease is now rare in these patients, measurement of bone mineral content by densitometry (DEXA) scanning usually indicates that bone loss is accelerated and the risk of osteoporotic fractures later in life is increased.

Box 43.8 Signs and symptoms in hyperparathyroidism

Anorexia, weight loss
Polydipsia, polyuria
Mental changes: poor concentration and memory
Fatigue
Nausea, dyspepsia and vomiting
Constipation
Hypertension
Renal stones
Conjunctival and corneal 'calcium' deposits
Bone pain and deformity
Pathological fractures

Investigations

Hypercalcaemia is the primary biochemical abnormality in primary hyperparathyroidism. Phosphate levels are often decreased and PTH levels are either inappropriately normal in the face of hypercalcaemia or elevated. In a patient with borderline elevation of calcium and a normal or only marginally elevated PTH, the benign condition familial hypocalciuric hypercalcaemia (FHH) must be excluded. Urine calcium excretion is increased in primary hyperparathyroidism and low in FHH.

There are many other causes of hypercalcaemia, including malignancy (including myeloma), drugs (thiazides, excess vitamin D), thyrotoxicosis, immobilisation and sarcoidosis. In all these situations, PTH levels are undetectable as the normal parathyroid glands appropriately switch off production of PTH in the face of hypercalcaemia. The most common cause of symptomatic hypercalcaemia in clinical practice is that associated with malignancy and this diagnosis must always be excluded.

Localisation of parathyroid tumours is only required in those listed for neck exploration. Most parathyroid surgeons request a neck ultrasound prior to performing a neck exploration. Isotope scanning, CT, MRI and selective venous sampling are reserved for those patients (around 1% in experienced hands) in whom the adenoma cannot be located at the first operation.

Treatment

Surgical removal of the adenoma or removal of all hyperplastic tissue is the only curative treatment for primary hyperparathyroidism; however, the natural history of hyperparathyroidism is not fully documented. Some studies have indicated that over 50% of untreated patients with primary hyperparathyroidism show no deterioration over 5 years, but the longer-term effects on renal function and bone mass

remain unknown. In practice, many patients are observed and their specific problems separately addressed. Thus, patients receive bisphosphonates for osteoporosis, anti-hypertensives, acid-lowering therapy and laxatives.

The main indications for surgical treatment are persistent hypercalcaemia > 2.85 mmol/L, symptomatic hypercalcaemia, renal impairment, renal stones and progression of osteoporosis. Postoperatively, temporary hypocalcaemia (hungry bones) is common. In patients with bone disease, treatment with alfacalcidol and calcium supplements should be started on the day before the operation. Approximately 10% of surgically treated patients develop permanent hyperparathyroidism.

Treatment of hypercalcaemia

Severe hypercalcaemia is a common medical emergency. It must be corrected whilst investigation continues to identify the cause. Table 43.7 shows the treatments available. In practice, rehydration and parenteral bisphosphonates, for example, pamidronate 60 mg in 250 mL normal saline over 30 min, will normalise calcium over 72 h in most patients.

Table 43.7 Treatment of hypercalcaemia

Mechanism	Treatment
Increase urinary calcium excretion	Normal saline plus loop diuretic
Reduce bone resorption	Bisphosphonates Calcitonin Gallium, mithramycin
Reduce gastro-intestinal absorption	Glucocorticoids in calcitriol dependent (vitamin D excess, sarcoid and some lymphoma patients)
Chelation Dialysis	Intravenous EDTA or phosphate

Case studies

Case 43.1

Mrs HP is a 49-year-old professional singer with Graves' disease. She was initially treated with carbimazole but developed a severe generalised rash, which necessitated withdrawal of the drug. A similar rash occurred within 2 weeks of starting PTU. She is overtly thyrotoxic with a blood pressure of 160/50 mmHg, a pulse of 110 beats/min and a large thyroid gland with a vascular bruit. Laboratory results show an elevated free T_4 and an undetectable TSH.

Questions

1. What are the options for treatment and what factors would you discuss with her that could influence her choice of treatment modality?
2. Mrs HP elects to have an ablative dose of radioactive iodine. What adjunctive therapy would you now consider?

Answers

1. This lady has experienced true allergic reactions to both available thionamide drugs and remains thyrotoxic. She should be counselled that thyroid ablation is required and that the treatment options include an ablative dose of radioactive iodine or thyroidectomy. It is necessary to consider features which would make surgery preferable. These would include concern about malignancy, features of local compression including difficulty swallowing or respiratory stridor, a large goitre causing cosmetic embarrassment or inability to receive radioiodine treatment (pregnancy, childhood). Radioactive iodine is more often an appropriate choice of treatment in patients who have either failed to achieve a remission with, or who have reacted adversely to, thionamides. It is known to be an entirely safe form of treatment though restrictions are placed on a patient for up to 1 month after the dose to reduce the public's exposure to radioactivity. Specific to this lady is her profession as a singer. She should be warned that surgery can rarely damage the recurrent laryngeal nerve leading to permanent hoarseness. This complication of surgery is often an important factor in choice of treatment for those who use their voice in their work (singers, actors, teachers, etc.).
2. To reduce the risk of inducing a thyroid crisis, attempts to render Mrs HP euthyroid before the dose of radioiodine should be made. If not asthmatic, she should be commenced on full doses of β-blockers. Propranolol-modified release is particularly useful as a once daily regimen will assist adherence and propranolol, unlike many other β-blockers, inhibits peripheral conversion of T_4 to T_3. Lithium should be commenced at 800 mg daily and will effectively reduce thyroid hormone secretion. Lithium has the useful added benefit of enhancing thyroidal retention of radioiodine and improving its efficacy in control of thyrotoxicosis in patients with large goitres.

Case 43.2

Mrs MG is a 66-year-old woman. She has a history of depression over many years and has recently been complaining of increased tiredness, lethargy and weight gain. Thyroid function tests have shown a TSH elevated at 12 mU/L (normal range, 0.3–5 U/L), but her free T4 is normal at 12.7 pmol/L (normal range, 10.5–25 pmol/L). Her TPO antibodies are positive at a dilution of 1:1600.

Questions

1. What is Mrs MG's thyroid state?
2. Should T_4 therapy be instituted, and if so, how should it be monitored?
3. What warnings should she receive about treatment?

Answers

1. Mrs MG has autoimmune thyroid disease and compensated hypothyroidism. The T_4 is being maintained in the normal range by virtue of increased TSH drive to the thyroid. Left alone, the disturbance is likely to get worse.
2. The British Thyroid Association has recommended that thyroxine treatment should be offered to patients with positive TPO antibodies whose TSH is above 10 mU/L and those whose TSH is between 5 and 10 who have symptoms which are compatible with hypothyroidism. Thyroxine should be commenced at 50 µcg daily and the dose adjusted along conventional lines by measurement of TSH at least 6 weeks after each dose change.

3. It is common for the non-specific symptoms of hypothyroidism to be mimicked by other conditions, notably depression. Mrs MG should be counselled that thyroxine treatment, though appropriate, may not reverse her symptoms and that if she remains symptomatic when her TSH has been normalised, alternative explanations for her symptoms will need to be considered.

Case 43.3

Mr DE is a 21-year-old man who has been treated for autoimmune hypothyroidism over 5 years. He is now prescribed thyroxine at 350 μcg daily, but his TSH has remained elevated varying between 24.4 and 68.2 mU/L. He also has alopecia areata which has had a very severe effect on his self-confidence and he has been seeing a private trichologist for advice.

Question

What are the possible causes of failure to satisfactorily treat his hypothyroidism?

Answer

The commonest cause of failure to suppress TSH is patient non-adherence with treatment. This is especially likely in a young patient with an irregular lifestyle and the elderly who are forgetful. Very few patients require as much as 350 μcg daily for an adequate replacement dose.

If assessment of the patient suggests that adherence is good, consideration must be given to malabsorption of thyroxine. This can be associated with inflammatory bowel disease or coeliac disease. A host of commonly prescribed drugs and medicines available over the counter may reduce thyroxine absorption. Amongst others, these include ferrous sulphate, some antacids and multivitamin preparations. In this patient, there may be other agents recommended by the trichologist which could affect thyroxine absorption.

Case 43.4

Mr JJ is 55 years old. Six years previously, he had a myocardial infarct complicated by ventricular tachycardia. He had an implantable defibrillator placed and has been taking amiodarone 200 mg daily. He is complaining of increasing exertional dyspnoea and weight loss. His free T_4 is returned at 99.1 pmol/L (normal range, 10.5–25 pmol/L) with a fully suppressed TSH confirming thyrotoxicosis.

Questions

1. How does amiodarone cause thyrotoxicosis?
2. What investigations should be considered?
3. How should he be managed?

Answers

1. Amiodarone-induced thyrotoxicosis (AIT) has two distinct causes. Type 1 AIT results from activation of latent autoimmune disease (Graves' disease) or nodular thyrotoxicosis, and is believed to be mediated by the high levels of iodine liberated through metabolism of the drug. Type 2 AIT is due to thyroiditis and results from release of pre-formed hormone. It is good practice to check a patient for thyroid autoantibodies and nodular disease prior to commencing amiodarone as patients with these markers are more likely to develop AIT.
2. It can be difficult to distinguish between type 1 and type 2 AIT. Patients should be referred urgently to a specialist endocrine unit. Thyroid autoantibodies should be requested along with an ultrasound of the thyroid, which will confirm nodular disease and will often show characteristic features of thyroiditis.
3. Type 1 AIT responds to thionamides. Type 2 AIT is treated with glucocorticoids. Amiodarone should be discontinued whenever possible, but since most patients have serious underlying coronary disease, this must only be done in conjunction with the patient's cardiologist. In practice, many patients are treated with both agents whilst awaiting the results of investigation and cardiology advice. For Type 2 AIT, if amiodarone can be discontinued, the thyroiditis usually resolves over a period of weeks. Otherwise, hypothyroidism will usually ensue and can be managed with thyroxine. For Type 1 AIT, if amiodarone cannot be stopped, thyroid ablation is required after control is achieved with thionamides. Since radioiodine uptake is characteristically low in patients receiving amiodarone, surgical removal may be necessary.

Case 43.5

Mrs BK is aged 76. During a routine assessment by her primary care doctor, her calcium is found to be 2.74 mmol/L (normal range, 2.25–2.60 mmol/L), her PTH is normal at 5.3 pmol/L (normal range, 1.5–6.5) and she has no symptoms. She has been taking weekly alendronate for osteoporosis over the past 4 years since sustaining a wrist fracture. Repeat DEXA scans have shown improved bone mineral density on this treatment. Review of her record discloses that her calcium was 2.67 at the time of her fracture, but at the time of her hysterectomy, when she was 45, her calcium was measured at 2.26 mmol/L.

Questions

1. Does she have primary hyperparathyroidism? Does she require any additional tests?
2. How should she be treated? What are the indications for neck exploration in primary hyperparathyroidism?

Answers

1. Yes, she has primary hyperparathyroidism. An elevated calcium with an inappropriately elevated PTH points to this diagnosis. If her parathyroid glands were normal, the PTH level would be undetectable in the face of the hypercalcaemia. It is very common for marginal hypercalcaemia to go unrecognised for many years in hyperparathyroidism. In the absence of the previous evidence of normocalcaemia from many years earlier, demonstration of an elevated urine calcium excretion would be required to provide reassurance that she does not have the inherited condition familial hypocalciuric hypercalcaemia (a benign and lifelong marginal elevation of calcium resulting from reduced sensitivity of the calcium sensing receptor in parathyroid cells). Since it is known that she once was normocalcaemic, no additional biochemical investigation is required though a renal scan should be arranged to rule out nephrocalcinosis.
2. Mrs BK can be reassured that no additional treatment is required at present. She should receive advice that her condition requires monitoring by annual calcium measurements and repeat DEXA scans to demonstrate continued response to alendronate. Absolute indications for neck exploration would include the presence of renal stone disease, progressive osteoporosis despite treatment, hypercalcaemic symptoms and calcium above 3.0 mmol/L. Relative indications include young age at diagnosis, a rising calcium over

2.8, osteoporosis or osteopaenia. A majority of patients with hyperparathyroidism can be satisfactorily treated medically.

Case 43.6

Ms JH is 22 years old when she is admitted to hospital after a grand mal convulsion. She is found to have a serum calcium of 1.15 mmol/L (normal range, 2.25–2.60) and an undetectable PTH. She has been very well with no recent symptoms of paraesthesiae or tetany, and has no other biochemical abnormalities.

Questions

1. What is the likely cause of her hypocalcaemia? Does she require any other tests?
2. How should she be treated?
3. What monitoring does she require?

Answers

1. She has hypoparathyroidism which is most likely to be autoimmune. Hypoparathyroidism can be associated with neck surgery, neck malignancy and infiltrative disease. Very rarely, it is due to embryonic failure of development of branchial arches, is congenital and is associated with severe immunological failure. The absence of any previous history in a fit young woman makes other causes of hypoparathyroidism exceedingly unlikely. The absence of symptoms of hypocalcaemia indicates that her calcium has been low for a long time and supports a relatively slowly progressive pathology. Rapid falls to this level (e.g. after neck surgery) are invariably associated with hypocalcaemic symptoms. It is very likely that her magnesium level will also be low, and this should be tested as it may also require treatment in the short-term.
2. The emergency treatment of hypocalcaemia is by regular i.v. infusions of 10% calcium gluconate with magnesium sulphate by slow i.v. infusion in patients with significant hypomagnesaemia. Ms JH will then need oral vitamin D analogues plus calcium supplements to maintain her calcium in the normal range. 1-alpha cholecalciferol is an effective and convenient preparation and the dose required ranges from 0.5 to 2 µcg daily.
3. Once her calcium has been normalised, she will need biochemical monitoring at a minimum of 6-month intervals. She should never be discharged as in some patients the calcium can drift above the normal range. If this is not identified, renal stone disease and renal failure can develop.

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Diabetes mellitus 44

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Key points

- Diabetes is a chronic, incurable condition with an estimated 2.6 million individuals diagnosed in the UK, equivalent to over 4% of the population. An estimated 2.3 million have type 2 disease, 0.3 million type 1 disease and another 500,000 are probably undiagnosed.
- Up to 15% of hospital in-patients will have diabetes.
- The cost of treating diabetes and its related complications, around £9 billion, equates to 10% of the total NHS budget.
- Effective control of diabetes (glycaemic levels, blood pressure, dyslipidaemia) reduces the risk of developing long-term complications and saves both lives and money.
- Abdominal fat is metabolically different from subcutaneous fat and is implicated in the development of insulin resistance and type 2 diabetes.
- Extreme hyperglycaemia and hypoglycaemia may lead to diabetic emergencies, both of which carry mortality risks.
- There is a wide variety of insulins and delivery devices available, allowing regimens to be tailored to individual need.
- Dietary modifications and oral medicines may maintain adequate glycaemic control in type 2 diabetes, but in time many patients will eventually require insulin.
- People with diabetes require education and support to enable them to effectively manage their disease, diet and lifestyle.

Box 44.1 Aetiological classification of diabetes mellitus

Type 1 (β-cell destruction, usually leading to absolute insulin deficiency)
Autoimmune
Idiopathic

Type 2 (may range from predominantly insulin with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)

Other specific types
Genetic defects of β-cell function
Genetic defects in insulin action
Diseases of the exocrine pancreas
Endocrinopathies
Drug or chemical induced, for example, nicotinic acid, glucocorticoids, high-dose thiazides, pentamidine, interferon-α
Infections
Uncommon forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes
Gestational diabetes

Diabetes mellitus is the most common of the endocrine disorders. It is a chronic condition, characterised by hyperglycaemia and due to impaired insulin secretion with or without insulin resistance. Diabetes mellitus may be classified according to aetiology, by far the most common types being type 1 and type 2 diabetes (Box 44.1). More than 2.6 million people in the UK have diabetes, and by the year 2025, this number is estimated to rise to 4 million.

Type 1 diabetes is a disease characterised by the destruction of the insulin-producing pancreatic β-cells, the development of which is either autoimmune T-cell mediated destruction (type 1A) or idiopathic (type 1B). In over 90% of cases, β-cell destruction is associated with autoimmune disease. Type 1 diabetes usually develops in the young (below the age of 30), although it can develop at any age and is usually associated with a faster onset of symptoms leading to dependency on extrinsic insulin for survival.

Type 2 diabetes is more common above the age of 40, with a peak age of onset in developed countries between 60 and 70 years, although it is being increasingly seen in younger people and even children. The prevalence of type 2 diabetes varies widely in different populations, being six times more common in those of South Asian origin compared with those of Northern European origin. It is caused by a relative insulin deficiency and insulin resistance. Symptoms are generally slower in onset and less marked than those of type 1. Type 2 diabetes may be an incidental finding, particularly when patients present with complications associated with the disease, for example, heart disease. Type 2 disease often progresses to the extent whereby extrinsic insulin is required to maintain blood glucose levels. The differences between type 1 and type 2 diabetes are highlighted in Table 44.1. It is sometimes difficult to distinguish clinically between type 1 and type 2 diabetes. The important thing to be aware of is that it is predominantly the degree of metabolic abnormality that is the key determinant of the form of treatment.

Two other varieties of non-typical diabetes that may be seen are latent autoimmune diabetes in adults (LADA) and maturity-onset diabetes of the young (MODY). LADA occurs in younger, leaner individuals who appear to have type 2 diabetes as they do not become ketotic and may manage without insulin for a time. Antiglutamic acid decarboxylase (GAD) antibodies may be present and the individual usually

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Table 44.1 Differences between type 1 and type 2 diabetes

Type 1 diabetes	Type 2 diabetes
β-cell destruction	No β-cell destruction
Islet cell antibodies present	No islet cell antibodies present
Strong genetic link	Very strong genetic link
Age of onset usually below 30	Age of onset usually above 40
Faster onset of symptoms	Slower onset of symptoms
Insulin must be administered	Diet control and oral hypoglycaemic agents often sufficient control
Patients usually not overweight	Patients usually overweight
Extreme hyperglycaemia causes diabetic ketoacidosis	Extreme hyperglycaemia causes hyperosmolar hyperglycaemic state

progresses to insulin more rapidly than those with other varieties of type 2 diabetes. MODY was noted over 30 years ago and described a subset of type 2 diabetes of young onset, often with a positive family history. Genetic studies have now identified this to be a monogenic autosomal dominant form of diabetes. MODY related to the glucokinase gene typically causes a resetting of the glucose level with a 'mild' non-progressive hyperglycaemia in which diet treatment is usually sufficient. Other types of MODY are related to mutations in the hepatocyte nuclear factor genes and usually develop during adolescence or the early 20s. Pharmacological treatment is required, but sulphonylureas are extremely effective and insulin can usually be avoided.

Epidemiology

The incidence of type 1 diabetes is increasing worldwide, for unknown reasons. It is speculated that environmental changes may be causing modification to the diabetes-associated alleles. Also, since the introduction of insulin in the 1930s, an increasing number of people with type 1 diabetes have had children. There are major ethnic and geographical differences in the prevalence and incidence of type 1 diabetes. Figures are highest in Caucasians (especially Scandinavians), while the disorder is rare in Japan and the Pacific area. In northern Europe, the prevalence is approximately 0.3% in those under 30 years of age. Type 1 diabetes may present at any age, but there is a sharp increase around the time of puberty and a decline thereafter. Approximately 50–60% of patients with type 1 will present before 20 years of age.

Type 2 diabetes is much more common than type 1, accounting for 90% of people with diabetes. It usually occurs in those over the age of 40 years. Estimates in the UK suggest that type 2 diabetes currently affects approximately 2.3 million people, and up to another 500,000 are thought to be undiagnosed. The incidence of type 2 rises with age and with increasing obesity. As with type 1, there are major ethnic and geographical variations. In general, in non-obese populations, the prevalence is 1–3%. In the more obese societies, there is a sharp increase in prevalence with estimates of 6–8% in the USA, increasing to values as high as 50% in the Pima Indians of Arizona. Diabetes is six times more common among Asian immigrants in the UK than in the indigenous population. World studies of immigrants have suggested that the chances of developing type 2 are between two and 20 times higher in well-fed populations than in lean populations of the same race.

Aetiology

Both genetic and environmental factors are relevant in the development of type 1 diabetes, but the exact relationship between the two is still unknown. There is a strong immunological component to type 1 and a clear association with many organ-specific autoimmune diseases. Circulating islet cell antibodies (ICAs) are present in more than 70% of those with type 1 at the time of diagnosis. Family studies have shown that the appearance of ICAs often precedes the onset of clinical diabetes by as much as 3 years. Type 1 has been widely believed to be a disease of clinically rapid onset, but the development is related to a slow process of progressive immunological damage. However, it is not currently possible to use screening methods to reliably identify patients who will develop diabetes in the future. The final event that precipitates clinical diabetes may be caused by sudden stress such as an infection when the mass of β-cells in the pancreas falls below 5–10%.

Studies have been carried out in which patients with newly diagnosed type 1 were treated with immunosuppressive therapies such as ciclosporin, azathioprine, prednisolone and antithymocyte globulin. When started soon after diagnosis, these therapies showed transient improvements in clinical measures and increased the rate of remissions in which insulin was not required. However, their use is limited in an otherwise healthy and young population due to potential toxicity and the risks associated with immune suppression.

Studies have investigated the use of anti-CD3 monoclonal antibodies. When newly diagnosed type 1 patients are treated with short courses of anti-CD3 monoclonal antibodies, smaller insulin doses are required. This relates to better preservation of β-cell function.

Type 2 diabetes also has a strong genetic predisposition. Identical twins have a concordance rate approaching 100%, suggesting the relative importance of inheritance over environment. If a parent has type 2, the risk of a child eventually developing type 2 is 5–10% compared with 1–2% for type 1. Type 2 diabetes occurs because of the progressive development of insulin resistance and β-cell dysfunction, the latter leading to an inability of the pancreas to produce enough insulin to overcome the insulin resistance. About 85% of people with type 2 diabetes are obese. This highlights the clear association

between type 2 and obesity, with obesity causing insulin resistance. In particular, central obesity, where adipose tissue is deposited intra-abdominally rather than subcutaneously, is associated with the highest risk. Body mass index (BMI) has been used as an indicator for predicting type 2 risk; however, it does not take fat distribution into account, so waist circumference measurements are now being increasingly used.

Pathophysiology

The islets of Langerhans form the endocrine component of the pancreas, constituting 1% of the total pancreatic mass. Insulin is synthesised in the pancreatic β-cells, initially as a polypeptide precursor, preproinsulin. The latter is rapidly converted in the pancreas to proinsulin. This forms equal amounts of insulin and C-peptide through removal of four amino acid residues. Insulin consists of 51 amino acids in two chains (the A chain contains 21 amino acids and B chain contains 30), connected by two disulphide bridges. In the islets, insulin and C-peptide (and some proinsulin) are packaged into granules. Insulin associates spontaneously into a hexamer containing two zinc ions and one calcium ion.

Glucose is the major stimulant to insulin release. The response is triggered both by the intake of nutrients and the release of gastro-intestinal peptide hormones. Following an intravenous injection of glucose, there is a biphasic insulin response. There is an initial rapid response in the first 2 min, followed after 5–10 min by a second response which is smaller but sustained over 1 h. The initial response represents the release of stored insulin and the second phase reflects discharge of newly synthesised insulin. Glucose is unique; other agents, including sulphonylureas, do not result in insulin biosynthesis, only release. Once released from the pancreas, insulin enters the portal circulation. The liver rapidly degrades it and only 50% reaches the peripheral circulation. In the basal state, insulin secretion is at a rate of approximately 1 unit/h. The intake of food results in a prompt five- to tenfold increase. Total daily secretion is approximately 40 units.

Insulin circulates free as a monomer, has a half-life of 3–5 min and is primarily metabolised by the liver and kidneys. In the kidneys, insulin is filtered by the glomeruli and reabsorbed by the tubules and degraded. In both renal and hepatic disease, there is a decrease in the rate of insulin clearance, which may necessitate dosage reduction for those using exogenous insulin. Peripheral tissues such as muscle and fat also degrade insulin, but this is of minor quantitative significance.

The interaction of insulin with the receptor on the cell surface sets off a chain of messengers within the cell. This opens up transport processes for glucose, amino acids and electrolytes.

In type 1 diabetes, there is an acute deficiency of insulin that leads to unrestrained hepatic glycogenolysis and gluconeogenesis with a consequent increase in hepatic glucose output. Also, glucose uptake is decreased in insulin-sensitive tissues such as adipose tissue and muscle; hence, hyperglycaemia ensues. Either as a result of the metabolic disturbance itself or secondary to infection or other acute illness, there is increased secretion of the counter-regulatory hormones glucagon, cortisol, catecholamine and growth hormone. All of these will further increase hepatic glucose production.

In type 2 diabetes, the process is usually less acute, since insulin production decreases over a sustained period of time. Hyperinsulinaemia is able to maintain glucose levels for a period of time, but eventually β-cell function deteriorates and hyperglycaemia ensues. If this cycle is not interrupted, type 2 diabetes develops. Impaired glucose tolerance (IGT), impaired fasting glucose or hyperinsulinaemia may be detected before overt diabetes develops, and if so, a strict diet and exercise regimen leading to weight loss and improved insulin sensitivity may delay or even prevent the onset of diabetes. At the time of diagnosis, those with type 2 diabetes may have already lost about 50% of their β-cell function. Irrespective of treatment, β-cell function continues to decline with time, often leading to the need for regular insulin therapy.

Type 2 diabetes is also associated with the metabolic syndrome (or syndrome X), although the real relevance of this 'syndrome' continues to be debated in the literature (Khan et al., 2005). The metabolic syndrome is a group of risk factors commonly found in those with type 2 diabetes, including insulin resistance, glucose intolerance (type 2 diabetes or IGT), hyperinsulinaemia, hypertension, dyslipidaemia, central obesity, atherosclerosis and increased levels of procoagulant factors, for example, plasminogen activator inhibitor-1 and fibrinogen.

Pathophysiology of insulin resistance

Abdominal fat, found in abundance in the majority of those with type 2 diabetes, is metabolically different from subcutaneous fat and can cause 'lipotoxicity'. Abdominal fat is resistant to the antilipolytic effects of insulin, resulting in the release of excessive amounts of free fatty acids, which in turn lead to insulin resistance in the liver and muscle. The effect is an increase in gluconeogenesis in the liver and an inhibition of insulin-mediated glucose uptake in the muscle. Both these result in increased levels of circulating glucose. Further, excess fat itself may contribute to insulin resistance because when adipocytes become too large they are unable to store additional fat, resulting in fat storage in the muscles, liver and pancreas, causing insulin resistance in these organs.

Excess intra-cavity adipose tissue causes the oversecretion of some cytokines (adipokines or adipocytokines) associated with inflammation, endothelial dysfunction and thrombosis. Examples of such adipokines include plasminogen activator inhibitor-1 (which is prothrombotic), tumour necrosis factor-α and interleukin-6 (which are proinflammatory) and resistin (which causes insulin resistance). The atherosclerosis associated with insulin resistance is due to hypercoagulability, impaired fibrinolysis and the toxic combination of endothelial damage (caused by chronic, subclinical inflammation), oxidative stress and hyperglycaemia. Excess adipose tissue is also thought to cause undersecretion of a beneficial adipokine called adiponectin. Adiponectin suppresses the attachment of monocytes to endothelial cells, thereby protecting against vascular damage. People with type 2 diabetes have lower levels of adiponectin than those without diabetes and weight reduction increases adiponectin levels.

Clinical manifestations

The symptoms of both type 1 and type 2 diabetes are similar, but they usually vary in intensity. Those associated with type 1 diabetes are more severe and faster in onset. The symptoms are related to the osmotic effects of glucose and the abnormalities of energy partitioning. Common symptoms include polyuria (increased urine production, particularly noticeable at night) and polydipsia (increased thirst). These are a consequence of osmotic diuresis secondary to hyperglycaemia. These symptoms are frequently accompanied by fatigue due to an inability to utilise glucose and marked weight loss because of the breakdown of body protein and fat as an alternative energy source to glucose. Blurred vision caused by a change in lens refraction may also occur and patients should be advised that as glucose levels are normalised, vision normally improves and new spectacles should be avoided for the first 3 months of effective treatment of the hyperglycaemia. Patients may also experience a higher infection rate, especially Candida, and urinary tract infections due to increased urinary glucose levels.

Type 1 diabetes

The metabolic abnormality at presentation of an individual with type 1 diabetes is often profound. The symptoms mentioned earlier are usually extreme and of recent (days or weeks) onset. In a significant proportion, the presenting symptoms are those of diabetic ketoacidosis, nausea, vomiting, dehydration, shortness of breath secondary to an attempt by the respiratory system to neutralise the metabolic acidosis caused by the ketones and, in extreme cases, coma.

Type 2 diabetes

Many patients with type 2 diabetes have an insidious onset of hyperglycaemia, with few or no classic symptoms. This is particularly true in obese individuals, whose diabetes may be detected only after glycosuria or hyperglycaemia is found serendipitously. Some patients are unaware of the disease even with marked classic symptoms as they begin so gradually and over such a long period of time. Recurring infections, for example, urinary tract, chest, soft tissue, are common because sustained hyperglycaemia can result in severe impairment of phagocyte function, and raised glucose levels provide a growth medium for bacteria.

Generalised pruritus and symptoms of vaginitis, which may be due to candidal infection, are frequently the initial complaints of women with type 2 diabetes. Patients often present when the complications of sustained hyperglycaemia have already developed, for example, cardiovascular disease or renal disease. Retinopathy may be detected on routine ophthalmological examination. Alternatively, a combination of neuropathy, peripheral vascular disease (PVD) and infection may manifest as foot ulceration or gangrene. In some cases, patients present with hyperosmolar hyperglycaemic state (HHS) where glucose levels in excess of 35 mmol/L are found and excessive dehydration has occurred. Occasionally, patients with type 2 diabetes present with diabetic ketoacidosis, especially in severe infection or in those of African/Caribbean descent.

Diagnosis

In June 2000, the UK formally adopted the World Health Organization criteria for diagnosing diabetes mellitus that was initially published in 1999. It has since been updated and the diagnostic criteria have been reiterated (World Health Organization, 2006).

1. Diabetes symptoms (i.e. polyuria, polydipsia and unexplained weight loss) plus:
   - a fasting serum glucose concentration ≥7.0 mmol/L
   - or serum glucose concentration ≥11.1 mmol/L 2 h after 75 g anhydrous glucose in an oral glucose tolerance test (see later).
2. With no symptoms, diagnosis should not be based on a single glucose determination but requires confirmatory serum venous determination. At least one additional glucose test result, on another day with the value in the diabetic range, is essential, either fasting or from the 2-h post-glucose load. If the fasting value is not diagnostic, the 2-h value should be used.

Current recommendations are that the diagnosis is confirmed by a glucose measurement performed in an accredited laboratory on a venous serum sample. A diagnosis should never be made on the basis of glycosuria or a stick reading of a finger prick blood glucose alone, although such tests are being examined for screening purposes. Glycated haemoglobin (HbA_{1c}) is also not currently recommended for diagnostic purposes, although this is currently being considered.

Glucose tolerance test

The patient should not be taking any drugs which interfere with glucose handling. A normal diet with at least 150 g of carbohydrate per day should be consumed for the 3 days before the test, but the patient should be fasted from 8 pm (except for water) on the day before the test. The test should commence at around 9 am with a venous serum glucose test, followed by the administration of 75 g of glucose by mouth over a 5-min period. This is often given in the form of 394 mL of Lucozade® original. The second venous serum glucose sample is then taken 2 h after the drink. The patient should be seated and is not permitted to smoke, eat or drink anything other than water until the test is complete. As there is a risk of later-onset hypoglycaemia in some individuals, it is advisable to suggest that the patient has something to eat immediately upon completion of the test, especially if he/she is planning to drive.

Diabetic emergencies

Hypoglycaemia and extreme hyperglycaemia, causing diabetic ketoacidosis or hyperosmolar hyperglycaemic state, constitute the three acute emergencies associated with diabetes.

Hypoglycaemia

Hypoglycaemia can occur both with insulin treatment and in those taking some oral agents, especially the longer-acting sulphonylureas, for example, chlorpropamide and glibenclamide. Definitions of hypoglycaemia vary, and in particular, there is no WHO definition. However, symptoms caused by the release of counter-regulatory hormones predominantly adrenaline (epinephrine), noradrenaline (norepinephrine) and glucagon tend to occur when the venous serum glucose drops below 3.0 mmol/L in healthy individuals. These symptoms described in Box 44.2 are a normal physiological response to hypoglycaemia and should alert the person to consume carbohydrates. Individuals may not respond appropriately to hypoglycaemia of this degree for several reasons, termed hypoglycaemia unawareness. First, the relevance of the symptoms has not been explained to them. This is an educational failing. It is imperative, therefore, that people with diabetes who are prescribed medication which is known to cause hypoglycaemia should be educated about the autonomic symptoms so that they may take action to avoid further decline of serum glucose. Second, the symptoms simply may not occur because of autonomic neuropathy. One of the commonest complications of diabetes is neuropathy, and when this includes the autonomic nervous system, there are no reliable symptoms to warn the individual that they are hypoglycaemic. A similar situation may occur as a consequence of drugs which suppress autonomic symptoms, such as β-blockers. Third, the patient may have recurrent hypoglycaemia. In those individuals who suffer frequent hypoglycaemic episodes, the autonomic symptoms may cease to occur. There is some evidence that the symptoms can be regained if, for a period of a few weeks, the serum glucose level can be maintained out of the hypoglycaemic range. Finally, the individual may be hypoglycaemia unaware because of alcohol intoxication.

If the serum glucose is allowed to drop to around 2 mmol/L, there are acute changes in cerebral function which lead initially to confusion. This is followed by coma, seizures and death if the glucose drops below about 0.5 mmol/L. Any cerebral malfunction is termed neuroglycopaenia.

Box 44.2 Symptoms of hypoglycaemia

Autonomic
Sweating
Trembling
Tachycardia
Palpitations
Pallor

Neuroglycopaenic
Faintness
Loss of concentration
Drowsiness
Visual disturbances
Abnormal behaviour (agitation, aggressiveness)
Confusion
Coma

Other
Hunger
Headache
Perioral tingling/numbness

Causes of hypoglycaemia

The most common causes of hypoglycaemia are either a decrease in carbohydrate consumption, excess carbohydrate utilisation from unexpected exercise or increase in circulating insulin (Table 44.2).

Nocturnal hypoglycaemia

Sometimes, hypoglycaemia occurs throughout the night. Symptoms may include restlessness, although this may not be identified unless observed by another person. When nocturnal hypoglycaemia occurs, the person often wakes feeling unrested, unwell or with a headache. Contrary to what might be expected, morning blood glucose readings may be high because

Table 44.2 Causes of hypoglycaemia

Cause	Comment
Missed meals or delays in eating	Reduced carbohydrate intake, therefore reduction in glucose levels
Not eating the usual amount of carbohydrates	Reduced carbohydrate intake, therefore reduction in glucose levels
Increased doses of insulin	Increased uptake of glucose into cells and increased storage of glucose as glycogen
Increased doses of oral insulin secretagogues	Increased levels of insulin therefore increased uptake of glucose into cells and increased storage of glucose as glycogen
Introduction of other blood glucose-lowering agents to oral insulin secretagogues	Enhanced hypoglycaemic effects
Increase in exercise	Increased uptake of glucose into cells
Excessive alcohol consumption	Impaired gluconeogenesis
Liver disease	Impaired gluconeogenesis and glycogenolysis

a sustained hypoglycaemic episode leads counter-regulatory hormones to raise blood glucose levels. This could present a confusing picture as the obvious solution to a raised blood glucose level in the morning would be to increase the evening/night-time dose of insulin. However, in the case of nocturnal hypoglycaemia, this would make the problem worse. If nocturnal hypoglycaemia is suspected, then blood glucose should be measured at night, for example, 2.00–3.00 am. If confirmed, the patient should either have a snack before bedtime, reduce the evening/night-time dose of insulin, alter the timing of administration of the evening dose of intermediate- or long-acting insulin in order to delay the peak of bioavailability or change the intermediate-acting insulin to a peakless analogue as appropriate. It is important to discuss nocturnal hypoglycaemia with patients as there is often a fear of dying from unrecognised hypoglycaemia in sleep. This fear is unfounded because of the protection from hypoglycaemia severe enough to cause death afforded by the counter-regulatory hormones. This occurs even in those individuals with autonomic neuropathy.

Treatment of hypoglycaemia

If the patient is able to swallow safely without the risk of aspiration, then glucose should be taken orally. However, if unable to swallow or if there is a risk of aspiration because, for example, of a decreased level of consciousness, parenteral treatment should be given, either intravenous glucose or intramuscular glucagon.

The most effective oral treatments are pure sources of glucose, for example, five glucose tablets or glucose drinks such as 150 mL of Lucozade®. In an emergency, hot drinks should be avoided as they might burn and drinks containing milk are not suitable as the fat in milk slows down sugar absorption. Blood glucose levels should be measured about 10–15 min after treating hypoglycaemia. If below 3.5 mmol/L, more glucose should be consumed. If above 3.5 mmol/L and the next meal will be over 1 h, then a long-acting carbohydrate is also required, for example, bread or biscuits. However, if the person is taking an α-glucosidase inhibitor such as acarbose, then monosaccharide carbohydrates must be given because disaccharides and polysaccharides will not be absorbed due to inhibition of the enzymes cleaving carbohydrate into absorbable monosaccharide units.

Should parenteral treatment be required, 25 g of intravenous glucose or 1 mg of intramuscular glucagon is recommended. Glucagon takes approximately 15–20 min to work, but if the person has liver disease (cirrhosis) or is malnourished, then glucagon may not work because glucagon acts by mobilising glucose stores from the liver. In such cases, intravenous glucose must be given. A number of serious extravasation injuries, some necessitating amputation of the affected limb, have been caused by 50% glucose. As a consequence, many hospitals now use 20% glucose.

Diabetic ketoacidosis

Diabetic ketoacidosis is serious, and in developed countries, it has a mortality rate of 5–10%. It occurs because absence of insulin causes extreme hyperglycaemia. At the same time, the normal restraining effect of insulin on lipolysis is removed. Non-esterified fatty acids are released into the circulation and taken up by the liver, which produces acetyl coenzyme A (acetyl CoA). The capacity of the tricarboxylic acid cycle to metabolise acetyl CoA is rapidly exceeded. Ketone bodies, acetoacetate and hydroxybutyrate are formed in increased amounts and released into the circulation. Further, osmotic diuresis, caused by hyperglycaemia, lowers serum volume, causing dizziness and weakness due to postural hypotension. Weakness is increased by potassium loss, caused by urinary excretion and vomiting due to stimulation of the vomiting centre by ketones, and catabolism of muscle protein. When insulin deficiency is severe and of acute onset, all of these symptoms are accelerated. Ketoacidosis exacerbates the dehydration and hyperosmolarity by producing anorexia, nausea and vomiting. As serum osmolarity rises, impaired consciousness ensues with coma developing in approximately 10% of cases. Metabolic acidosis causes stimulation of the medullary respiratory centre, giving rise to Kussmaul respiration (deep and rapid breathing) in an attempt to correct the acidosis. The patient's breath may have the fruity odour of acetone (ketones) commonly described as smelling like pear drops or nail varnish remover.

Precipitating factors for diabetic ketoacidosis in type 1 disease are usually omission of insulin dose, acute infection, trauma or myocardial infarction. Although diabetic ketoacidosis is normally associated with type 1 diabetes, it may rarely occur in people with type 2.

Diagnosis of diabetic ketoacidosis

Diagnosis requires demonstration of hyperglycaemia and metabolic acidosis with the presence of ketones. The biochemical diagnosis of ketoacidosis is usually made at the bedside and confirmed in the laboratory. Urinalysis will show marked glycosuria and ketonuria. A blood glucose test strip usually shows a blood glucose level of more than 22 mmol/L. Formal laboratory measurement of glucose, urea, creatinine, electrolytes and venous bicarbonate should be carried out. Two potentially misleading laboratory results are the white blood cell count and serum sodium. The former will always be raised but correlates with the ketone body level and is not therefore a guide to infection. The serum sodium level will often be low due to the osmotic effect of glucose draining water from the cells and diluting the sodium. The sodium concentration will also be spuriously low if there is marked dyslipidaemia.

Treatment of diabetic ketoacidosis

Treatment comprises fluid volume expansion (initially with 0.9% sodium chloride), correction of hyperglycaemia and the presence of ketones (by infusion of insulin), prevention of hypokalaemia, and identification and treatment of any associated infection. Once the patient is better, they should be reviewed by the diabetes team in order to discuss how to avoid future episodes of diabetic ketoacidosis.

Hyperosmolar hyperglycaemic state

HHS is associated with type 2 disease and has a higher mortality rate (15%) than diabetic ketoacidosis. HHS usually occurs in middle-aged or elderly people, about 25% of whom have previously undiagnosed type 2 diabetes.

In HHS, unlike diabetic ketoacidosis, there is no significant ketone production and therefore no severe acidosis. Hyperglycaemia occurs gradually over a sustained period of time, leading to dehydration due to osmotic diuresis which, if severe, results in hyperosmolarity. Hyperosmolarity may increase blood viscosity and the risk of thromboembolism. Factors precipitating HHS are infection, myocardial infarction, poor adherence with medication regimens or medicines which cause diuresis or impair glucose tolerance, for example, glucocorticoids.

Diagnosis of HHS

The diagnostic features of HHS are hyperglycaemia (often in the region of 55 mmol/L, which is generally much higher than for diabetic ketoacidosis), dehydration and hyperosmolarity. There may be a mild metabolic acidosis but without marked ketone production. Conscious levels on presentation range from slight confusion to coma. In some cases, seizures occur. Serum sodium and potassium levels are usually normal, but creatinine is high. The average fluid deficit is 10 L, so circulatory collapse is common.

Treatment of HHS

Treatment requires fluid replacement to stabilise blood pressure and improve circulation and urine output. Sodium chloride 0.9% or 0.45% (if serum sodium is greater than 150 mmol/L) is given and monitoring of blood pressure and cardiovascular status undertaken. Potassium may be added if required. Insulin treatment is started via intravenous infusion but is not aggressive, since fluid replacement also lowers serum glucose levels. Prophylaxis or treatment for thromboembolism may also be required.

Long-term diabetic complications

Diabetes and its long-term complications cost the NHS substantial amounts of money – approximately 10% of the total budget (£173 million/week).

Although all long-term complications may occur in each type of diabetes, the spectrum of incidence is different. Many patients with type 2 diabetes have had their disease a long time before the diagnosis, by which time many have developed diabetic complications (Figs. 44.1 and 44.2). However, diabetic complications can be limited and sometimes prevented altogether if good management occurs from an early stage. Hyperglycaemia and hypertension are the two major modifiable risk factors that influence the development of diabetic complications.

Patients with diabetes should undergo regular review of their disease management for early signs of associated complications and review of these risk factors and their management. Diabetic complications are frequently divided into macrovascular and microvascular complications. Macrovascular complications arise from damage to large blood vessels and microvascular complications occur from damage to smaller vessels. The general aetiology of macro- and microvascular

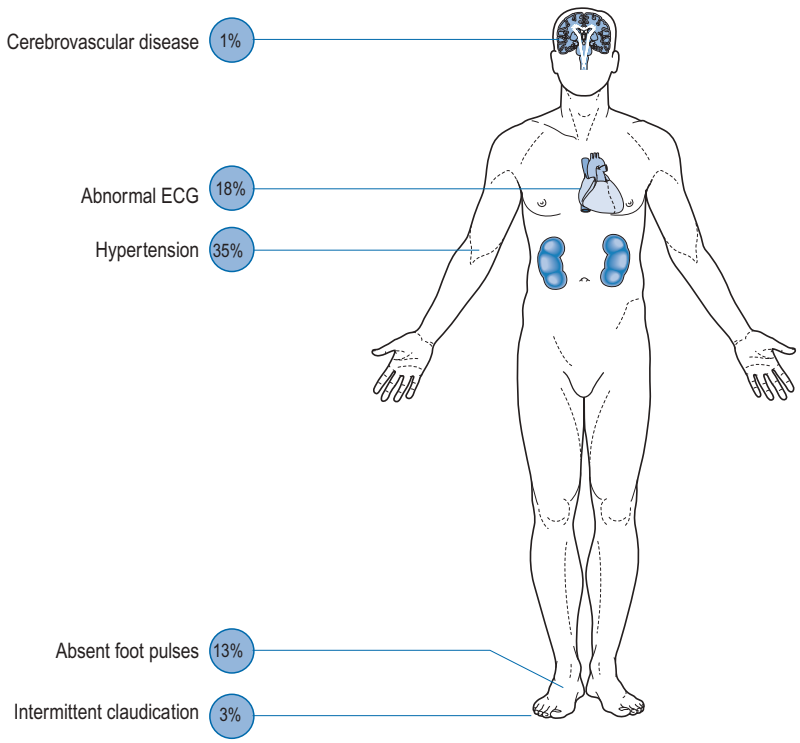


Fig. 44.1 Incidence of macrovascular complications at diagnosis in type 2 diabetes.

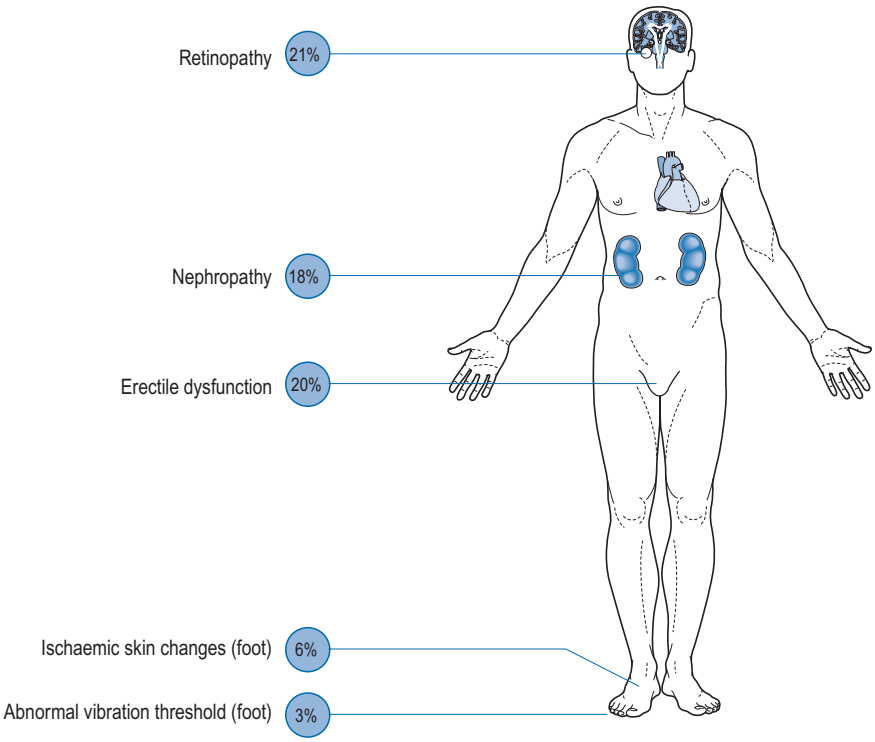


Fig. 44.2 Incidence of microvascular complications at diagnosis in type 2 diabetes.

complications is the same and results from atherosclerosis of the vessels, which may lead to occlusion. The main aims of treatment are, first, to prevent the immediate symptoms associated with diabetes, for example, polyuria, polydipsia, etc., and second, to prevent development, or slow the progression of the long-term disease complications.

Macrovascular disease

The risk of macrovascular complications, including cardiovascular disease (coronary heart disease and stroke) and PVD, is 2–4 times higher for people with diabetes.

Cardiovascular disease

The most common cause of death in people with type 2 diabetes is cardiovascular disease which accounts for an estimated 80% of deaths in this patient group. The risk of a person with diabetes having a myocardial infarction (MI) is the same as someone without diabetes having a second myocardial infarction. The risk of cardiovascular disease is increased further if nephropathy is present. Other cardiovascular disease risk factors are the same as in the non-diabetic population and include smoking, hypertension and dyslipidaemia. However, these risk factors are enhanced in the presence of diabetes, and therefore smokers are encouraged to stop, and individuals with hypertension and lipid disorders are actively reviewed and treated. Silent myocardial infarction (infarction with no symptoms) is more common in those with diabetes and may be due to cardiac autonomic neuropathy. Cerebrovascular disease is also more commonly associated with diabetes, and patients have a greater mortality and morbidity compared to the general population.

Hypertension. Hypertension is twice as common amongst the diabetic population compared to the general population. It affects over 80% of those with type 2 diabetes. The treatment target ranges for people with diabetes are generally lower than for people without diabetes, as hypertension is associated with the development of macro- and microvascular complications. For people with type 2 diabetes, hypertension is a feature of the metabolic syndrome and is associated with insulin resistance. For those with type 1 disease, it is closely associated with renal disease.

Peripheral vascular disease

PVD affects the blood vessels outside the heart. In people with diabetes, it often affects the arteries of the legs and may give rise to intermittent claudication, a cramping pain experienced on walking, due to reversible muscle ischaemia secondary to atherosclerosis. The iliac vessels can be affected, causing buttock pain and also erectile dysfunction. If PVD is present, the risk of cardiovascular disease increases. About 20% of people with PVD die from myocardial infarction within 2 years of symptom onset.

PVD is also responsible for much of the morbidity associated with diabetic foot problems.

Microvascular disease

Microvascular complications include retinopathy, nephropathy and neuropathy.

Retinopathy

Diabetic retinopathy is the leading cause of blindness in people under the age of 60 in industrialised countries. Twenty years from the onset of diabetes, over 90% of people with type 1, and over 60% of people with type 2, will have diabetic retinopathy. The main problem with diagnosing retinopathy is that it is symptomless until the disease is far advanced. Therefore, if regular screening is not undertaken, diagnosis may not be made early enough for successful treatment intervention. Tight glycaemic control has been shown to prevent and delay the progression of retinopathy in patients with type 1 disease. Likewise, for patients with type 2 diabetes, both tight glycaemic control and tight blood pressure control reduce the risk of developing retinopathy. When retinopathy is detected early, sight may be saved by laser photocoagulation. In advanced cases, surgery may be required.

Pregnancy may worsen moderate-to-severe retinopathy, particularly if there is poor or sudden improvement in glycaemic control. However, tight glycaemic control during pregnancy reduces the long-term risks of retinopathy.

Nephropathy

In diabetic renal disease, the kidneys become enlarged and the glomerular filtration rate (GFR) initially increases. However, if the nephropathy progresses, the GFR starts to decline. Serum creatinine used alone to estimate renal function has limitations. The GFR can be estimated (eGFR). The most popular method is the modified Modification of Diet in Renal Disease (MDRD) formula, which requires serum creatinine, age, sex and ethnicity:

$$\text{eGFR} = 175 \times [\text{plasma creatinine } (\mu\text{mol/L}) \times 0.011312]^{1.154} \times [\text{age in years}]^{0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$$

$$\text{eGFR} = \text{glomerular filtration rate } (\text{mL/min per } 1.73\,\text{m}^2)$$

The presence of nephropathy is indicated by the detection of microalbuminuria (small amounts of albumin present in urine). If higher amounts of albumin are detected, this is termed proteinuria (or macroalbuminuria) and signifies more severe renal damage. Microalbuminuria is defined as an albumin:creatinine ratio (ACR) greater or equal to 2.5 mg/mmol (men) and 3.5 mg/mmol (women). Proteinuria may be defined as an albumin:creatinine ratio greater than 30 mg/mmol or albumin concentration greater than 200 mg/L. Proteinuria may progress to end-stage renal disease and require dialysis. Albumin in the urine increases the risk of cardiovascular disease, with microalbuminuria associated with 2–4 times the risk, proteinuria with nine times the risk and end-stage renal disease increasing risk by 50 times.

Tight control of both glycaemic levels and blood pressure reduces the risk of developing nephropathy. Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) are the treatments of choice, since both have been demonstrated to provide renal protective effects additional to their antihypertensive effects. ACE inhibitors and ARBs have been shown to delay the progression to proteinuria in patients with microalbuminuria. Although not proven for all individual drugs in these classes, it is considered to be a class effect. However, these drugs should be used with care if there is a risk of renovascular disease.

Peripheral neuropathy

Peripheral neuropathy is the progressive loss of peripheral nerve fibres resulting in nerve dysfunction. Diabetic neuropathies can lead to a wide variety of sensory, motor and autonomic symptoms. The most common is the symmetrical distal sensory type, which is particularly evident in the feet and may slowly progress to a complete loss of feeling. It is most prevalent in elderly patients with type 2 diabetes but may be found with any type of diabetes, at any age beyond childhood. Painful diabetic neuropathy is another manifestation of sensory neuropathy; it can be extremely disabling and may cause considerable morbidity. Guidance on the treatment of painful neuropathy is available (National Institute for Health and Clinical Excellence, 2010). Diabetic proximal motor neuropathy is rapid in onset and involves weakness and wasting, principally of the thigh muscles. Muscle pain is common and may require opiate analgesia. Distal motor neuropathy can lead to symptoms of impaired fine co-ordination of the hands and/or foot slapping.

Autonomic neuropathy may affect any part of the sympathetic or parasympathetic nervous systems. The most common manifestation is diabetic impotence. Bladder dysfunction usually manifests as loss of bladder tone with a large increase in volume. Diabetic diarrhoea is uncommon, but can be troublesome as it tends to occur at night. Gastroparesis may cause vomiting and delayed gastro-intestinal transit and variable food absorption, causing difficulty in the insulin-treated patient. Postural hypotension due to autonomic neuropathy is uncommon but can be severe and disabling. Disorders of the efferent and afferent nerves controlling cardiac and respiratory function are more common, but rarely symptomatic. Autonomic neuropathy may also cause dry skin and lack of sweating, both of which may contribute to diabetic foot problems.

Macro- and microvascular disease combined

Diabetic foot problems

Infected diabetic foot ulcers account for the largest number of diabetes-related hospital bed-days and are the most common non-trauma cause of amputations. The rate of lower-limb amputation in people with diabetes is 15 times higher than in the general population. The lifetime risk of a person with diabetes developing a foot ulcer is around 15%. Diabetic foot ulcers are a costly problem and are associated with considerable morbidity. Foot problems often develop as a result of a combination of specific problems associated with having diabetes, that is sensory and autonomic neuropathy, PVD and hyperglycaemia. Poor foot care and poorly controlled diabetes are also contributory factors. Development of foot

ulcers may be partly preventable by patient education. People with diabetes learn that their feet are particularly vulnerable, and if problems arise, they must seek immediate professional advice.

There are three main types of foot ulcers: neuropathic, ischaemic and neuroischaemic. Neuropathic ulcers occur when peripheral neuropathy causes loss of pain sensation. The ulcers can be deep but are usually painless and are caused by trauma to the foot which is not noticed until after significant damage has occurred. Ischaemic ulcers result from PVD and poor blood supply causing a reduction in available nutrients and oxygen required for healing. Ischaemic ulcers are painful and usually occur on the distal ends of the toes. Most ulcers have elements of both neuropathy and ischaemia and are termed neuroischaemic.

Diabetic foot ulcers are prone to infection, the most common pathogens being staphylococci and streptococci. Wounds with an ischaemic component are commonly infected with anaerobic organisms.

Charcot arthropathy. This is an uncommon foot complication caused by severe neuropathy. It results in chronic, progressive destruction of joints with marked inflammation. Reduced bone density leads to bone fractures, altered foot shape and gross deformity. Owing to the deformity which occurs, excess pressure over protruding bone frequently leads to ulceration unless footwear is extensively modified.

Treatment

Treatment for people with diabetes includes advice on nutrition, physical activity, weight loss and smoking cessation if appropriate. Drug therapy is prescribed where necessary.

Structured education programmes

It is now considered standard care to offer people with diabetes education to help them manage their diabetes themselves on a day-to-day basis. This should be offered in a structured way and based upon theories of adult learning. Group education is now invariably offered as it offers economic advantages over one-to-one education as well as peer support. Examples of such programmes include DAFNE (Dose Adjustment For Normal Eating) in type 1 diabetes and DESMOND (Diabetes Education for Self Management in the Ongoing and Newly Diagnosed) in type 2 diabetes.

Diet

Dietary control is the mainstay of treatment for type 2 diabetes and plays an integral part in the management of type 1. Dietary recommendations have undergone extensive review in recent years and considerable changes have been made. Generally speaking, healthy eating advice for people with diabetes is the same as for the general population. Some of the general dietary advice that patients should be given is shown in Box 44.3.

Box 44.3 General dietary advice for people with diabetes

- Eat regular meals based on starchy foods such as bread, pasta, potatoes, rice and cereals. Whenever possible, choose high-fibre varieties of these foods, for example, wholemeal bread and wholemeal cereals which have a lower glycaemic index.
- Try to cut down on fat, particularly saturated (animal) fats. Monounsaturated fats such as olive oil are preferred. Use less butter, margarine, cheese and eat fewer fatty meals. Choose low-fat dairy foods, for example, skimmed milk and low-fat yoghurt. Grill, steam or oven bake instead of frying or cooking with oil or other fats.
- Try to eat at least five portions of fruit and vegetables every day. This provides vitamins and fibre as well as helping to balance the overall diet.
- Cut down on sugar and sugary foods. Sugar can still be used as an ingredient in foods and baking as part of a healthy diet. Use sugar-free, low-sugar or diet squashes and fizzy drinks, as sugary drinks cause blood glucose levels to rise quickly.
- Use less salt as high intake can raise blood pressure. Food can be flavoured with herbs and spices instead of salt.
- Drink alcohol in moderation. Two units/day for a woman and three for a man. A small glass of wine or half a pint of normal strength beer is one unit. Never drink on an empty stomach as alcohol can exacerbate hypoglycaemia.

Carbohydrates and sweeteners

The blood glucose level is closely affected by carbohydrate intake. Previous guidance for people with diabetes recommended eating about the same amount of carbohydrate at approximately the same time each day and generally advised restriction of carbohydrates. As a consequence of this advice, a number of people tended to eat more fat. Current guidance for carbohydrate consumption still emphasises the importance of total carbohydrate intake, but it focuses on selecting carbohydrates with a lower glycaemic index, that is carbohydrates which give sustained release of sugars over time, as opposed to carbohydrates with a high glycaemic index that give high peaks in blood glucose concentration. Examples of carbohydrates with a low glycaemic index include beans, pulses and starchy foods like wholemeal pasta and wholegrain bread. Total carbohydrate consumption should not exceed 45–60% of energy intake, with monounsaturated fat and carbohydrate combined making up 60–70% of energy intake.

Sucrose or 'sugar' may be included in the diet, according to the new guidance, but sucrose should account for no more than 10% of total energy and should be spaced throughout the day, rather than being consumed all in one go. Sugar alcohols, for example, sorbitol, maltitol and xylitol, often used as sugar substitutes in diabetic foods, are expensive and may cause diarrhoea. They are therefore considered to confer little advantage over sucrose. Non-nutritive or intense sweeteners such as aspartame, saccharin, acesulphame K, cyclamate and sucralose may be useful, especially for those who are overweight.

Alcohol. Alcohol contains carbohydrates and, if consumed in excess, may cause hyperglycaemia. However, more dangerously, it is also associated with later-onset (up to 16 h post-alcohol) hypoglycaemia and hypoglycaemia unawareness.

Alcohol must be restricted to the same maximum weekly quantities as for the general population, that is, 14 units (women) and 21 units (men), with 1–2 alcohol-free days per week. In these quantities, alcohol has cardioprotective effects.

Fats

Since obesity is a major problem in type 2 diabetes and fats contain more than twice the energy content per unit mass than either carbohydrate or protein, consumption of fats should be limited. Monounsaturated fats have a lower atherogenic potential and are therefore recommended as the main source of dietary fat. Intake of fat should be less than 35% of total energy consumption, with saturated and trans-unsaturated fats accounting for less than 10% of energy intake and monounsaturated fats providing 10–20%.

Examples of monounsaturated fats are olive oil and rapeseed (also known as canola) oil. Saturated fats are chiefly of animal origin, for example, beef, pork, lamb, whole milk products with some found in plants, for example, cocoa butter, coconut oil and palm oil. Trans-unsaturated fats are found in hydrogenated vegetable oils and hard margarines. N-6 polyunsaturated fats such as cornflower, sunflower, safflower, soyabean oil and seed oils should account for less than 10% of energy intake, and n-3 polyunsaturated fats (fish oils) should be eaten as fish, rather than fish oil supplements, once or twice a week.

Protein

For adults without nephropathy, protein intake is recommended as less than 1 g/kg of body weight, equivalent to about 10–20% of total energy intake. For those with nephropathy, protein intake may need to be further restricted, but this requires expert dietetic advice and supervision.

Fibre

There is no quantitative dietary recommendation for fibre intake. Dietary fibre has useful properties in that it is physically bulky, and it delays the digestion and absorption of complex carbohydrates, thereby minimising hyperglycaemia. For the average person with type 2 diabetes, 15 g of soluble fibre from fruit, vegetables or pulses is likely to produce a 10% improvement in fasting blood glucose, glycated haemoglobin and low-density lipoprotein cholesterol (LDL-C). Insoluble fibre from cereals, wholemeal bread, rice and pasta has no direct effect on glycaemia or dyslipidaemia, but it has an overall benefit on gastro-intestinal health and may help in weight loss by promoting satiety.

Salt

Sodium chloride should be limited to a maximum of 6 g/day. A reduction in salt intake from 12 to 6 g/day has been shown to produce a reduction in systolic blood pressure of 5 mmHg and a reduction of 2–3 mmHg in diastolic pressure.

Obesity management in type 2 diabetes

Obesity management is a very important issue in type 2 diabetes owing to the insulin resistance which occurs as a consequence of excess adipose tissue. Whilst any loss of weight in those who are overweight or obese is of benefit in diabetes in that it is associated with an improvement in dyslipidaemia, hypertension and glycaemic control, bariatric surgery can lead to profound improvements. Recent studies have shown that laparoscopic banding can induce remission of type 2 diabetes in 48% of individuals and Roux-en-y bypass procedures can induce remission in 84%. More importantly, bariatric surgery is associated with a 92% relative risk reduction in diabetes-specific mortality and consequently should be offered to those with diabetes who have a BMI of 35 kg/m^2 or higher (National Institute for Health and Clinical Excellence, 2006). For those with a BMI of 28 kg/m^2 or greater, it is recommended that the pancreatic and gastric lipase inhibitor, orlistat, be considered as the modest weight reduction which can be achieved with this agent yields benefits in diabetes control.

Insulin therapy in type 1 diabetes

All patients with type 1 diabetes require treatment with insulin in order to survive. Exogenous insulin is used to mimic the normal physiological pattern of insulin secretion as closely as possible for each individual patient. However, a balance is required between tight glycaemic control and hypoglycaemia risk. If the risk of hypoglycaemia is high, then it may be necessary to aim for less tight glycaemic control. There is a wide variety of insulin preparations available which differ in species of origin, onset of action, time to peak effect and duration of action (Table 44.3).

Species of origin

Until the 1980s, insulin was obtained and purified from the pancreas of pigs and cows. Human sequence insulins have subsequently been developed using recombinant DNA technology and are now the most common insulins in use. Many of the animal-derived products have been withdrawn, but some animal insulins continue to be available. Porcine insulin only differs from human insulin in one amino acid at the end of the B chain (position B30). Human insulin may be produced semi-synthetically by enzymatic modification of porcine insulin (emp). However, most human insulin is manufactured using genetic engineering and recombinant DNA technology. This is done by inserting either synthetic genes for the insulin A chain and B chain, or the proinsulin gene, or a proinsulin-like precursor into *Escherichia coli* (crb, prb) or yeast cells (pyr). The cells are fermented, resulting in large amounts of the recombinant protein, which is then converted into insulin and purified. More recently, human insulin analogues have been developed through genetic and protein engineering, to produce insulin molecules with differing pharmacokinetic properties.

It is now standard practice to commence all patients requiring insulin on human insulin. In those who have been changed from animal to human insulin, there has been concern that

Table 44.3 Insulin preparations

Preparation	Origin	Onset (h)	Peak (h)	Duration (h)
Soluble insulin				
Human Actrapid (pyr)	H	0.5	2–5	8
Humulin S (prb)	H	0.5	1–3	5–7
Hypurin Bovine Neutral	B	0.5/1	2–5	6–8
Apidra (insulin glulisine)	H	0.25	1	3–4
Humalog (insulin lispro)	H	0.25	1–1.5	2–5
Novorapid (insulin aspart)	H	0.25	1–3	3–5
Hypurin Porcine Neutral	P	0.5/1	2–5	6–8
Insuman Rapid (crb)	H	0.5	1–3	7–9
Biphasic insulin				
Humulin M3 (prb)	H	0.5	1–8.5	14–15
NovoMix 30	H	0.25	1–4	Up to 24 h
Humalog Mix 25	H	0.25	1–2	22
Humalog Mix 50	H	0.25	1–2	22
Hypurin Porcine 30/70	P	0.5	4–12	24
Insuman Comb 15 (prb)	H	0.5	2–4	12–20
Insuman Comb 25 (prb)	H	0.5	2–4	12–19
Insuman Comb 50 (prb)	H	0.5	1–4	12–16
Isophane insulin				
Hypurin Porcine Isophane	P	2	6–12	24
Insuman Basal (crb)	H	1	3–4	12–20
Human Insulatard (pyr)	H	2	4–12	24
Humulin I (prb)	H	0.5	2–8	18–20
Hypurin Bovine Isophane	B	2	6–12	24
Insulin zinc suspension (mixed)				
Hypurin Bovine Lente	B	2	8–12	30
Protamine zinc				
Hypurin Bovine PZI	B	4	10–20	36
Long-acting analogues				
Lantus (insulin glargine)	H	2–4	No peak	20–24
Levemir (insulin detemir)	H	2–4	6–14	16–20

Insulin preparations classified as being of human (H), beef (B) or pork (P) origin; prb, proinsulin recombinant bacteria; crb, chain recombinant bacteria; pyr, precursor yeast recombinant.

human insulin may be associated with an increased risk of hypoglycaemic unawareness, although current evidence suggests that this is unlikely if the switch is done appropriately. Human insulin may be more potent dose for dose than animal insulin due to the formation of antibodies. Conventionally, doses are reduced by 25% or more when changing from animal to either human or analogue insulin.

Insulin preparations

The onset of action, peak effect and duration of action are determined by the insulin type and by the physical and chemical form of the insulin.

Fast-acting insulins. Conventional fast-acting insulins are soluble insulins (also known as neutral insulins). After subcutaneous injection, soluble insulin appears in the circulation within 10 min. The concentration rises to a peak after about 2 h and then declines over a further 4–8 h. This absorption curve can be contrasted with the physiological insulin concentration curve, where peak concentrations are reached 30–40 min after a meal and decline rapidly to 10–20% of peak levels after about 2 h.

The fast-acting recombinant insulin analogues (insulin lispro, insulin aspart and insulin glulisine) are more rapidly absorbed than the non-analogue soluble insulins and have a shorter duration of action. The analogues therefore offer more flexibility. They are more convenient for some patients as they can be given immediately before a meal rather than the 30 min before recommended for human soluble insulin. Another benefit is a reduced risk of hypoglycaemia because of the shorter duration of action. These pharmacokinetic differences arise as the short-acting analogues remain as monomers (single units) unlike regular soluble human insulins which self-associate into a hexameric (6-unit) form. Hexamers need to

dissociate into dimers and monomers to be readily absorbed from subcutaneous tissue, which causes delayed absorption.

Intermediate-acting insulins. Conventional intermediate-acting insulins are insoluble, cloudy suspensions of insulin complexed with either protamine (also known as isophane or NPH insulin) or zinc (lente insulin).

Over time, insulin dissociates from the protamine, which gives the preparation its extended activity. The onset of action is usually 1–2 h with the peak effect being seen at 4–8 h. There is considerable inter-patient variation in the duration of action, but it usually requires twice-daily administration to adequately cover a 24-h period. Protamine insulin and soluble insulin do not interact when mixed together. Therefore, ready-mixed (biphasic) preparations are available containing both isophane and soluble insulin.

Long-acting insulins. More recently, long-acting insulin analogues such as insulin glargine and insulin detemir have been developed using recombinant DNA technology. They both have a duration of action of about 24 h, a more predictable, flat profile of action with no pronounced peaks and less inter- and intra-subject dosing variability.

Insulin glargine differs from human insulin as two arginine molecules have been added to the B chain at the C-terminal end. This alters the isoelectric point from pH 5.4 to 6.7. Also, the neutral amino acid glycine replaces the asparagine residue at position A21. The changes mean that insulin glargine remains soluble at a slightly acidic pH. The product is buffered at a pH of 4. Once it is injected into subcutaneous tissue, it forms a microprecipitate in the more neutral surrounding pH. This allows slow absorption from the injection site.

Insulin detemir has a long duration of action and is formulated at neutral pH. It differs from human insulin by omission of the amino acid threonine at position B30 and the attachment of a fatty acid chain (myristic acid) to lysine at position B29. The modification allows the insulin molecule to reversibly bind to albumin, via the fatty acid chain, following absorption from subcutaneous injection. This reduces the amount of free, active insulin detemir (bound insulin is inactive). The long duration of action is produced by dissociation of the insulin molecule from albumin.

Insulin delivery

All the currently licensed insulin products are available only by injection. An inhaled insulin product available for a short period of time is no longer obtainable. The subcutaneous route is routinely used for maintenance therapy, as opposed to the intravenous route which is sometimes used in hospital. Insulin can be injected subcutaneously into the outer aspect of the thigh, abdominal wall, buttocks or upper arm. However, injecting into the arm is incredibly difficult and is therefore not usually a site of choice. The main advantages associated with subcutaneous injection are accessibility, which allows most patients to administer their own insulin. However, this route cannot be regarded as physiological as it delivers insulin to the systemic rather than portal circulation.

A small number of patients still use disposable plastic syringes with insulin from a vial as their means of insulin administration, although the vast majority now use pen injection devices. Insulin pens may either be refillable or disposable. Although not in themselves improving diabetic control, they are popular amongst users since they are compact and more convenient as they remove the need to draw up insulin from a vial.

Intravenous insulin delivery should be used in the management of ketoacidosis and hyperosmolar states. The intravenous route is also preferable for diabetic patients due to have major surgery and who may be 'nil by mouth' after surgery. The short half-life of insulin (3–5 min) means that changes in infusion rate have a rapid effect on insulin action and glycaemic control. Intravenous insulin is commonly delivered as either a continuous insulin infusion at a variable rate or an infusion made with a fixed amount of insulin, with glucose and potassium in the same bag. The former is also commonly referred to as a 'sliding scale' insulin regimen, in which the rate of infusion is adjusted according to frequent blood glucose readings, usually hourly. It is administered with a co-infusion of glucose (with potassium, unless patient is hyperkalaemic). The latter type of insulin infusion is known as GKI (glucose, potassium, insulin), GIK or the Alberti regimen. Intravenous insulin regimens are not routinely recommended for patients who are eating and drinking.

Insulin regimens

Standard insulin regimens for managing type 1 disease vary between two to five injections daily. They must be tailored to the individual patient and will depend on lifestyle, willingness to achieve the best control and ability to cope with both injecting insulin and subsequent monitoring of blood glucose. The chosen insulin regimen is negotiated between patient and health care professional and may change throughout life according to priorities and patient preference. Starting doses of insulin and the ratio of short- to intermediate-acting insulin are very variable. In patients who are very active, such as manual workers and those who exercise regularly, the starting dose should be kept low to reduce the risk of significant hypoglycaemia.

Mealtime plus basal regimens. The best control for type 1 diabetes may be attained using a mealtime plus basal regimen, also referred to as a basal-bolus regimen. This mimics normal physiological insulin release more closely than other regimens. A mealtime plus basal regimen requires mealtime injections of insulin with a fast-acting preparation, preferably with an analogue, plus one or two injections of a basal (intermediate- or long-acting) insulin. This may require up to five injections a day. As a general rule, with this regimen, the soluble insulin injections given before each meal usually comprise 40–60% of the total daily dosage. Some individuals may benefit from exogenous insulin delivery via a continuous subcutaneous insulin infusion administered via a pump worn on their person. The pump can be programmed to give a different basal rate of infusion at different times of day, and boluses are then provided by the pump at mealtimes. There are specific indications for pump therapy (National Institute for Health and Clinical Excellence, 2008).

These regimens offer the most flexibility of dosing and eating habits, and often better blood glucose control. A number of patients have been taught to count mealtime carbohydrates and calculate their own insulin dose on the basis of the preprandial blood glucose concentration, which allows greater scope for 'normal eating'. An example is the DAFNE (dose adjusted for normal eating) programme (DAFNE Study Group, 2002), in which patients are required to attend structured, group education on five consecutive days.

The disadvantage of mealtime plus basal regimens is that they require multiple injections, unless a pump is *in situ*, and require regular blood glucose monitoring and the ability of the patient to match insulin doses according to carbohydrate intake, exercise levels and prevailing glucose levels. For some people, this is either too difficult or unsuitable.

Twice-daily regimens. The mealtime plus basal regimen may be too hard for some, for example, school-age children, to manage. In this type of situation, a twice-daily regimen may be more suitable. The simplest and most effective twice-daily regimens use premixed insulin, comprising a short- or rapid-acting plus an intermediate-acting insulin. Regular human insulin mixes and analogue mixes are available. The regular human insulin mixes should be given 30 min before breakfast and 30 min before the evening meal, whereas analogue mixes may be given immediately before these meals. The longer-acting component of the insulin mix given at breakfast time must span the lunchtime meal and the evening dose must bridge the night time. Twice-daily regimens using intermediate- or long-acting insulins alone are not sufficient for maintenance control of type 1 diabetes. Occasionally, they are used in newly diagnosed patients who are not acutely ill, adding the short-acting preparation if and when indicated by self-monitoring.

Adjusting the insulin dose

The information on which insulin dosage adjustment is based should be derived from blood glucose self-monitoring and the incidence and timing of hypoglycaemia. On twice-daily fast- and intermediate-acting insulin regimens, the soluble insulin may be considered as acting up to the next meal or to bedtime, while the extended-acting insulins act up to the next injection. The glucose concentration at the end of the period can be taken as a measure of the appropriateness of the relevant dose.

Adjustments to a dose of insulin should depend on the degree of insulin resistance present. In order to determine a suitable adjustment dose, the effect of other dosage adjustments in the same patient should be taken into consideration, as should the total insulin dose. For example, a 2-unit dose increase in someone taking 6 units of insulin would be a 33% dosage increase; however, a 2-unit dose increase in someone taking 60 units of insulin would be proportionately much less and make less impact.

Storage of insulin

Insulin formulations are stable if kept out of light, and they are not subject to freezing or extremes of heat. Loss of potency of 5–10% occurs in vials kept at high ambient room temperatures for 2–3 months. Insulin should therefore be stored in a domestic refrigerator except for the vial(s), cartridge(s) or pens in current use which, depending on the individual preparation, may be stable for 4–6 weeks (see manufacturers' recommendations). When pen injector devices are in use, they should never be stored in a refrigerator as there have been reports of devices 'seizing up' when stored in the cold. Also, the injecting of cold or refrigerated insulin is undesirable because it is more painful and the insulin absorption profile is altered.

Adverse effects of insulin

Hypoglycaemia is a common physiological complication of insulin therapy and is often a source of great anxiety to patients and carers. The symptoms (see Box 44.2) may occur at different blood glucose levels in different individuals.

Thickening of subcutaneous tissues can occur at injection sites because of recurrent injection in the same area, known as lipohypertrophy. As well as looking unsightly, it can result in impaired and erratic insulin absorption, leading to poor glycaemic control. The solution is to rotate injection sites. Bruising is usually a sign of superficial injections. Localised skin reactions occasionally occur but resolve even with continued use of the same insulin preparation.

Systemic allergic reactions rarely occur with the current universal use of highly purified insulins. Though not usually species specific, it is worthwhile trying insulin of a different species if allergy occurs. Also, some patients may experience allergy to the excipients within the insulin product or to the needle used for administration. If this is suspected, it is helpful to seek the advice of an immunologist and try an insulin product with different excipients.

Management of type 2 diabetes

About 80% of patients with type 2 diabetes are overweight at diagnosis, and this is known to cause insulin resistance. This means that higher doses of medication may be required to control blood glucose levels. Advice on weight loss through increased physical exercise and calorie restriction, in addition to education about general healthy eating, is required. Targets for weight should be to maintain a normal BMI of between 20 and 25 kg/m^2 or a waist circumference of less than 88 cm in women and 102 cm in men, which lowers the risk of developing insulin resistance. In those who are already overweight or obese, however, an achievable target of 10–15% body weight loss should be discussed as, if achieved, this will have significant benefits in overall diabetes control.

Some people are able to normalise their glycaemic control by weight loss and attention to diet (diet controlled). Nevertheless, such individuals still invariably have diabetes and are at risk of developing diabetic complications. Hyperglycaemia may still occur, especially in times of stress or if dietary control is lost, and consequently they should be monitored regularly.

For over 75% of people with type 2 diabetes, dietary measures and exercise alone do not produce adequate glycaemic control and oral hypoglycaemic therapy is required. Within

3 years of diagnosis, a large majority of patients will require oral drug therapy. In the UK, there are six classes of oral agents currently available: a biguanide (metformin), sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide), meglitinides (repaglinide and nateglinide), a thiazolidinedione (pioglitazone), an α-glucosidase inhibitor (acarbose) and the dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin and vildagliptin).

Acarbose has been poorly tolerated in trials, with only 39% of those receiving the drug still taking it after 3 years. The main reason for non-adherence appears to be flatulence. Acarbose is rarely prescribed in the UK but is popular in other countries such as Germany. Metformin remains the cornerstone of oral treatment for type 2 diabetes. The sulphonylureas and meglitinides are known as insulin secretagogues, since they both enhance secretion of insulin from the pancreatic β-cells. The relatively recent introduction of the dipeptidyl peptidase inhibitors (DPP-4 inhibitors) has been welcomed and is a useful new class of drug, particularly for those in whom weight is a problem, since they do not cause weight gain like many of the other drug treatments. Likewise, the incretin mimetics, another new class of injectable drugs, are often helpful for the obese population since they are associated with weight reduction.

In type 2 diabetes, the progressive decline in β-cell function with time and increasing insulin resistance means people with this disease show a progressive loss of glycaemic control and usually require two or three drugs to maintain control before ultimately requiring insulin.

The factors used to select a particular treatment include the patient's clinical characteristics, such as their degree of hyperglycaemia, weight and renal function (Fig. 44.3). In acutely ill people with significant hyperglycaemia, insulin therapy may well be required, albeit transiently because acute illness leads to an increase in stress hormones, all of which are anti-insulin.

Biguanides

Metformin is the only biguanide available in the UK. The mechanism of action of biguanides is still not completely understood. However, the principal mode of action is via potentiation of insulin action at an unknown intracellular locus, resulting in decreased hepatic glucose production by both gluconeogenesis and glycogenolysis. Metformin also stimulates tissue uptake of glucose, particularly in muscle, and is thought to reduce gastro-intestinal absorption of carbohydrate. The action of metformin does not involve stimulation of pancreatic insulin secretion and therefore it is still a beneficial agent when β-cell function has declined. Another advantage of metformin over insulin secretagogues, and sulphonylureas, in particular, is that it does not cause hypoglycaemia and is not associated with weight gain. Metformin has a short duration of action, with a half-life of between 1.3 and 4.5 h, and does not bind to serum proteins. It is not metabolised and is totally renally eliminated.

It has been shown that diabetes-related death was reduced by 42% in overweight subjects who took metformin for 10 years, compared to those who took conventional therapies such as a sulphonylurea or insulin. Myocardial infarction was also reduced by 39% over the 10-year follow-up period. Consequently, metformin has become the first-line therapy for glycaemic control when oral agents are indicated especially in overweight and obese patients.

Adverse effects. The most common adverse effects of metformin, affecting about a third of patients, result from gastro-intestinal disturbances including anorexia, nausea, abdominal discomfort and diarrhoea. In some patients, diarrhoea can be extreme and can preclude metformin use. However, the gastro-intestinal side effects are usually transient and can be minimised by starting with a low dose, increasing the dose slowly and administering the drug with or after food. A suggested regimen is to start with 500 mg daily for 1 week, then 500 mg twice daily for 1 week, increasing the dosage at weekly intervals until the desired glycaemic response is achieved or intolerance occurs. The maximum licensed dose is 3 g/day, but doses of more than 2 g/day often cause intolerance. If the initial dose of 500 mg daily causes side effects, then some prescribers reduce the starting dose to 250 mg daily for a week. This may be difficult for some patients as the 500 mg strength tablets are not scored and are not easy to halve.

Two modified-release metformin preparations are now available and permit once-daily dosing. Clinical evidence suggests that these formulations cause fewer problems with gastro-intestinal side effects. The maximum licensed dose of the modified-release preparations (2 g daily) differs from the standard preparation.

The two previously available biguanides, phenformin and buformin, were withdrawn due to deaths associated with lactic acidosis. Lactic acidosis is a rare complication with metformin, with an estimated incidence of five cases per 100,000 patient-years. However, it is potentially life threatening. Patients at most risk are those with renal insufficiency in whom the drug accumulates, individuals with co-existing conditions where lactate accumulates, and those who are unable to metabolise lactate. In practice, metformin should not be prescribed for patients who have renal impairment (eGFR <45 mL/min/1.73 m^2) and should be stopped in anyone with an eGFR <30 mL/min/1.73 m^2. Metformin should also be stopped in severe liver disease, uncontrolled cardiac failure or severe pulmonary insufficiency. It should be withdrawn in patients with severe intercurrent illness, for example, acute myocardial infarction or septicaemia, or those undergoing major surgery or requiring investigation using radiographic contrast media and should only be restarted once renal function has been evaluated and determined as within acceptable limits.

Role of metformin. Metformin is useful in obese patients with diabetes as it does not cause weight gain. If there are no contraindications, it can be used in conjunction with diet as second-line therapy in patients not adequately controlled on diet alone. As it has a different mode of action to the sulphonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors and DPP-4 inhibitors, it can be valuable when prescribed in combination.

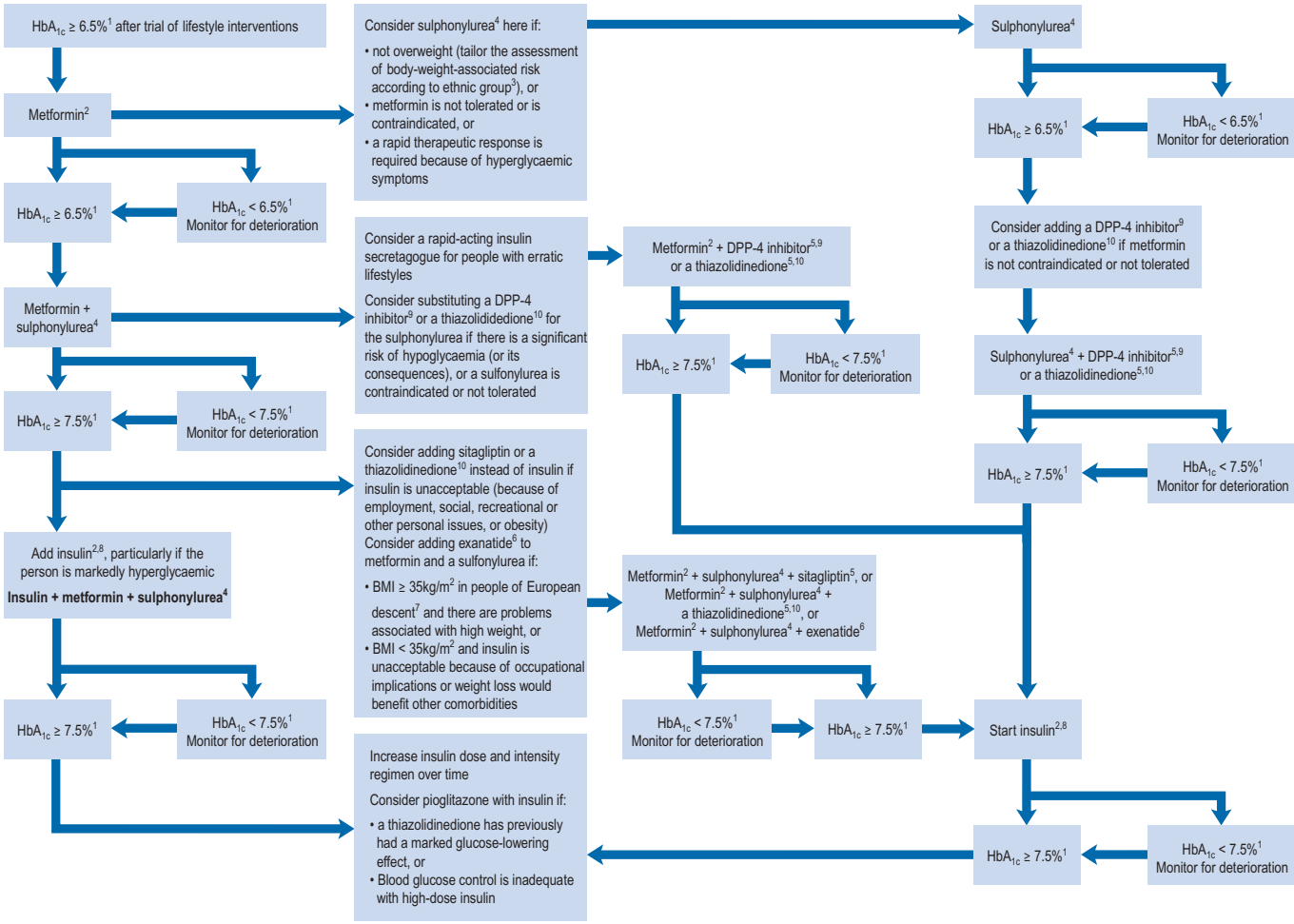


Fig. 44.3 Algorithm for the treatment of glycaemic control in type 2 diabetes. (1) or individually agreed target, (2) with active dose titration (3) see the NICE clinical guideline on obesity (www.nice.org.uk/CG43), (4) offer once-daily sulphonylurea if adherence is a problem, (5) only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA_{1c} of at least 0.5 percentage points in 6 months, (6) only continue exenatide if reduction in HbA_{1c} of at least 1 percentage point and weight loss of at least 3% of initial body weight in 6 months, (7) with adjustment for other ethnic groups, (8) continue with metformin and sulfylurea (and acarbose if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulphonylurea if hypoglycaemia occurs, (9) DPP-4 inhibitor refers to saxagliptin, sitagliptin or vidagliptin, (10) thiazolidinedione refers to ploglitazone.

Sulphonylureas

Mode of action. The major action of this class of drug relies on the ability of the pancreas to secrete insulin and hence requires functioning β-cells to exert a beneficial effect. Sulphonylureas lower blood sugar by increasing pancreatic β-cell sensitivity to glucose, allowing more insulin to be released from storage granules for a given glucose load. Sulphonylurea therapy is also associated with increased tissue sensitivity to insulin, resulting in improved insulin action. Studies also suggest that sulphonylureas may promote an increased systemic bioavailability of insulin due to reduced hepatic extraction of the insulin secreted from the pancreas.

Pharmacokinetics. The pharmacokinetic parameters of oral hypoglycaemic agents are shown in Table 44.4. Chlorpropamide is the slowest and longest acting agent, but it is now very rarely used. Although glibenclamide has been shown to have a short elimination half-life, it has a prolonged biological effect, which may be explained by slower distribution and the existence of a deep compartment, possibly the islet cells. All sulphonylureas are metabolised by the liver to some degree and some may have active metabolites.

Choice of drug. There are many factors which influence the choice of sulphonylurea. These may relate to the drug itself, the patient or the prescriber. There are few well-controlled long-term clinical comparisons between sulphonylureas. It would appear that, when dosage is individualised and governed by the effect on fasting blood glucose, there is little or no difference in clinical efficacy between different agents. In general, if a patient is not well controlled on the maximum dosage of one sulphonylurea, it is not worthwhile changing to another one.

Adverse effects. The frequency of adverse effects from sulphonylureas is low. They are usually mild and reversible on

Table 44.4 Pharmacokinetic properties of oral hypoglycaemic agents

Drug	Main route of elimination	Elimination half-life (h)	Duration of action (h)	Daily dose range	Doses per day
Sulphonylureas					
First generation					
Tolbutamide	Hepatic	4–24	6–10	0.5–2 g	1–3
Chlorpropamide	Hepatic (80%) Renal (20%)	24–48	24–72	100–500 mg	1
Second generation					
Glibenclamide	Hepatic (40%) Biliary (60%)	2–4	16–24	2.5–15 mg	1–2
Glipizide	Hepatic	2–4	6–24	2.5–40 mg	1–3
Gliclazide	Hepatic	10–12	10–24	40–320 mg	1–2
Glimepiride	Renal (60%) Biliary (40%)	5–8	12–24	1–6 mg	1
Biguanides					
Metformin	Renal	1–5	5–8	1–3 g	2–3
Meglitinides					
Repaglinide	Hepatic	1	4–6	1–16 mg	3 (with each main meal)
Nateglinide	Hepatic	1	3–4	180–540 mg	3 (with each main meal)
Thiazolidinediones					
Pioglitazone	Hepatic	5–6	16–24	15–30 mg	1
Dipeptidyl pepidase-4 inhibitors					
Sitagliptin	Renal	10–12	12–24	100 mg	1
Vildagliptin	Renal	3	10–12	50 mg	1–2
Saxagliptin	Renal and hepatic	2–3	At least 24 h	5 mg	1
Incretin mimetics					
Exenatide	Renal	2–3	Data not available	5–10 mcg	2
Liraglutide	No main organ identified	13	Data not available	0.6–1.8 mg	1

drug withdrawal (Table 44.5). The most common adverse effect is hypoglycaemia, which may be profound and long lasting. Hypoglycaemia due to sulphonylureas is often misdiagnosed, particularly in the elderly. The major risk factors for the development of hypoglycaemia include use of a long-acting agent, increasing age, renal or hepatic dysfunction and inadequate carbohydrate intake. The major side effect is, however, weight gain.

Other adverse effects are rare; blood dyscrasias occur in 0.1% of patients and rashes in up to 3%. Chlorpropamide can produce troublesome flushing after ingestion of alcohol, and about 5% of patients develop hyponatraemia due to its effect on increasing renal sensitivity to antidiuretic hormone (ADH). Most patients are asymptomatic with this problem, but occasionally severe hyponatraemia is observed. However, as mentioned earlier, this agent is no longer used in routine practice.

Sulphonylurea dosage. The dosage should be individualised for each patient. The lowest possible dose required to attain the desired levels of blood glucose, without producing hypoglycaemia, should be used. Treatment should start with a low dose and be increased if necessary approximately every 2 weeks. For many agents, the maximum effect is seen if the dose is taken half an hour before a meal, rather than with or after food. The number of daily doses required will depend on the agent used and the total daily dose. For several drugs, it becomes necessary to administer the drug two or three times daily when the dose is increased.

A modified-release preparation of gliclazide is available. A dose of 30 mg of the modified-release product is equivalent to 80 mg of the standard-release preparation.

Drug interactions. Several drugs can interfere with the efficacy of sulphonylureas by influencing either their pharmacokinetics or pharmacodynamics, or both. Despite much literature about displacement interactions with sulphonylureas, the clinical significance is doubtful. Many reported cases involve first-generation agents, which have a different protein-binding site from the second-generation agents, which bind in a non-ionic fashion and are not readily displaced. Ingestion of alcohol can cause hypoglycaemia in itself and can also prolong the hypoglycaemic effect of sulphonylureas.

Table 44.5 Adverse effects of sulphonylureas

Adverse effect	Comments
Gastro-intestinal	Affects approximately 2% Most commonly nausea and vomiting Dose related Advise patient to take with or after food
Dermatological	Affects 1–3% Usually occur within the first 2–6 weeks Most commonly: generalised photosensitivity, pruritus, maculopapular rash May require discontinuation of drug Cross-sensitivity between sulphonylureas is common Rare cases of severe allergic reactions, for example, erythema multiforme Stevens–Johnson syndrome
Haematological	Rare cases of fatal agranulocytosis or pancytopenia Other haematological effects usually reversible on discontinuing drug Some reports of reversible haemolytic anaemia
Hepatic	Mild, reversible elevation of liver function tests Cholestatic jaundice Usually a hypersensitivity reaction associated with fever, rash and eosinophilia
Cardiovascular	Possible excess of cardiovascular mortality in patients treated with tolbutamide (not proven)
Hypothyroidism	Association not proven May be rare cases
Alcohol flush	Rarely seen with sulphonylureas other than chlorpropamide Change to another agent
Syndrome of inappropriate antidiuretic hormone (SIADH)	Chlorpropamide and, to a lesser extent, tolbutamide enhance the effect of ADH on the kidney Results in hyponatraemia Risk factors are increasing age, congestive cardiac failure and diuretic therapy
Hypoglycaemia	The most common adverse effect and may be severe and prolonged Highest incidence with chlorpropamide and glibenclamide All sulphonylureas and meglitinides have been implicated Risk factors include increasing age, impaired renal or hepatic function, reduced food intake, weight loss Decrease dose, change to a shorter-acting agent or discontinue sulphonylurea therapy

Meglitinides

The meglitinides are insulin-releasing agents (insulin secretagogues), also called 'post-prandial glucose regulators'. They are characterised by a more rapid onset and shorter duration of action than sulphonylureas. Their site of action is pharmacologically distinct from that of the sulphonylureas. Repaglinide, a benzoic acid derivative, was the first member of the class. It is licensed for use as a single agent when diet control, weight reduction and exercise have failed to regulate glucose levels, or in combination with metformin. Nateglinide was introduced later and is a derivative of the amino acid d-phenylalanine. Nateglinide is only licensed for combination therapy with metformin when metformin alone is inadequate.

Mode of action. Like the sulphonylureas, the meglitinides stimulate first-phase insulin secretion by inhibiting ATP-sensitive potassium channels in the membrane of the pancreatic β-cells. This causes depolarisation and gating of the calcium channels (which are voltage sensitive), increasing the intracellular concentration of calcium and stimulating insulin release. The release of insulin only occurs in the presence of glucose. As glucose levels drop, less insulin is secreted. Conversely, if carbohydrates are consumed and glucose levels rise, insulin secretion is enhanced.

Pharmacokinetics. The pharmacokinetic properties of the meglitinides confer a rapid onset and a short duration of action. The individual parameters are shown in Table 44.4. The meglitinides are extensively metabolised in the liver, repaglinide by oxidative biotransformation and direct conjugation with glucuronic acid. The cytochrome P450 enzymes CYP2C8 and CYP3A4 have been shown *in vitro* to be involved its metabolism. Nateglinide is metabolised predominantly by cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP3A4. Repaglinide has no active metabolites, but nateglinide has partially active metabolites, one-third to one-sixth the potency of the parent compound. The meglitinides should be taken immediately before main meals, although the time can

vary up to 30 min before a meal. The pharmacokinetic profile of meglitinides offers some advantages in patients with poor renal function or irregular eating habits.

Adverse effects. The meglitinides may cause a range of side effects, most commonly hypoglycaemia, visual disturbances, abdominal pain, diarrhoea, constipation, nausea and vomiting. More rarely, hypersensitivity reactions can occur as well as elevation of liver enzymes. The meglitinides may also cause weight gain.

Dosage. The recommended starting dose for repaglinide is 500 μcg before or with each meal, increasing as necessary (depending on blood glucose measurements) every 1–2 weeks to a maximum single dose of 4 mg and a maximum daily dose of 16 mg. When patients are transferred from other therapies, the recommended starting dose is 1 mg preprandially. The recommended starting dose of nateglinide is 60 mg three times a day before meals, which may be subsequently increased to 120 mg three times a day. The maximum single dose is 180 mg, which may be given with the three main meals of the day.

Drug interactions. Drugs which induce or inhibit the cytochrome P450 enzymes CYP2C8 and CYP3A4 interact with repaglinide. Examples of drugs which enhance or prolong the hypoglycaemic effect include gemfibrozil, clarithromycin, ketoconazole, itraconazole, trimethoprim, other hypoglycaemic drugs, monoamine oxidase inhibitors, non-selective β-blockers, ACE inhibitors, salicylates, NSAIDs, octreotide, alcohol and anabolic steroids. Drugs which induce cytochrome P450 enzymes may also interact, for example, rifampicin and phenytoin, and may decrease repaglinide serum levels. Drugs that inhibit CYP2C9 may interact with nateglinide. Drugs that may enhance or prolong the hypoglycaemic effect include ACE inhibitors, gemfibrozil and fluconazole. The hypoglycaemic effects of nateglinide may be reduced by diuretics, corticosteroids and β-blockers.

Role of meglitinides. The meglitinides are an effective hypoglycaemic therapy in type 2 diabetes. They may be most beneficial in patients who experience problems with post-prandial glucose elevation and as single therapy in patients who eat at unpredictable times or have a tendency to miss meals. However, no outcome studies have been undertaken, and so their long-term use has not been proven to be more effective than the less expensive sulphonylureas. Therefore, their exact place in therapy is currently unclear.

Thiazolidinediones

Research into the action of the thiazolidinediones, also known as glitazones, has led to greater understanding of the development of type 2 diabetes. Only one glitazone, pioglitazone, is currently available following the removal of rosiglitazone from the UK market in 2010. Pioglitazone has been shown to have a significant benefit on macrovascular morbidity and mortality, demonstrating the benefit of a glucose-lowering agent on macrovascular disease (Dormandy et al., 2005).

Mode of action. The glitazones act as agonists of the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is mostly expressed in adipose tissue but is also found in pancreatic β-cells, vascular endothelium and macrophages. It is also expressed weakly in those tissues that express predominantly PPAR-α, for example, skeletal muscle, liver and heart. The thiazolidinediones lower fasting and post-prandial glucose levels in addition to lowering free fatty acid and insulin concentrations. They enhance insulin sensitivity and promote glucose uptake and utilisation in peripheral tissues. They also suppress gluconeogenesis in the liver and, by increasing insulin sensitivity in adipose tissue, suppress free fatty acid concentrations. In addition, patients with IGT have shown increased insulin secretory responses. However, they do not have a direct effect on insulin secretion. The indirect effects of glitazones on adipose tissue are due to alterations in the regulation of gene expression. Various adipokines (adiponectin, tumour necrosis factor-α, resistin and 11β-hydroxysteroid dehydrogenase 1) are regulated by PPAR-γ agonists in animal studies. Other effects of glitazones on the vasculature include antiatherogenic effects thought to be caused by a reduction in the inflammatory response, decrease in vasoconstriction and an increase in plaque stability.

Pharmacokinetics. Pioglitazone is metabolised extensively in the liver to both active and inactive metabolites (see Table 44.4).

Adverse effects. Pioglitazone has been associated with weight gain and oedema, particularly in patients with hypertension and congestive cardiac failure. Since the thiazolidinediones can lead to a worsening of heart failure that may be fatal, pioglitazone should not be used in patients with a previous history of or pre-existing heart failure. Combination therapy with insulin and thiazolidinediones has been found to result in a higher incidence of oedema. There is also an increased risk of bone fracture with pioglitazone, and it should be used with caution in post-menopausal women. Anaemia occurs in about 1% of patients and is seen as a small decrease in the haemoglobin concentration during the first 4–12 weeks of therapy. However, it is suggested this decrease is due to dilutional effects caused by an increase in serum volume. Pioglitazone caused weight gain of around 3.5 kg during clinical trials. Some patients also experience headache, abdominal pain, myalgia and upper respiratory infection. Pioglitazone may also elevate liver transaminases.

Rosiglitazone was withdrawn from the UK market because use was associated with an increased risk of cardiovascular disorders, including heart attacks and heart failure. Another thiazolidinedione, troglitazone, was withdrawn from the UK market in 1997 because of liver failure linked to a toxic metabolite of troglitazone.

Dosage. Pioglitazone is started at a dose of 15 mg or 30 mg and may be increased to 45 mg once daily. In combination with metformin or a sulphonylurea, the current dose can be continued. Administration of pioglitazone may be either with or without food. Dosage adjustment is not necessary in patients with mild or moderate renal impairment or in the elderly. However, neither agent should be used in patients with severe renal impairment or in those with hepatic impairment.

Drug interactions. Pioglitazone is metabolised by cytochrome P450 CYP3A4. Therefore, drugs which induce or

inhibit this enzyme interact with pioglitazone. Ketoconazole, itraconazole, erythromycin and fluconazole increase serum concentrations, while rifampicin and phenytoin decrease serum levels of pioglitazone.

Role of thiazolidinediones. Thiazolidinediones improve glycaemic control in patients, especially in those with insulin resistance, by reducing HbA_{1c} levels up to 1.5% compared to sulphonylurea or metformin alone.

Glitazones should be used as third-line therapy after life style modification and the use of metformin or a sulphonylurea as monotherapy. However, if glycaemic control remains poor, pioglitazone can be used either with metformin if treatment with a sulphonylurea is unsuitable, with a sulphonylurea if treatment with metformin is unsuitable, or with metformin and a sulphonylurea if insulin is unsuitable (National Institute for Health and Clinical Excellence, 2009). Treatment should only be continued if, after 6 months of treatment, the HbA_{1c} has reduced by 0.5% of its starting value.

Monotherapy with a thiazolidinedione may be a valuable treatment option for patients who are known to be insulin resistant. Triple therapy can be an alternative to transferring a patient to insulin, but the modest reduction in HbA_{1c} usually means that many patients will eventually require insulin. It is important to be aware that owing to their mode of action involving changes in gene transcription, thiazolidinediones take up to 3 months to have their maximum effect on glycaemic control.

α-glucosidase inhibitors

Acarbose reduces carbohydrate digestion by interfering with gastro-intestinal glucosidase activity. Although overall carbohydrate absorption is not significantly altered, the post-prandial hyperglycaemic peaks are markedly reduced. Acarbose is minimally absorbed in unchanged form from the gastro-intestinal tract.

Adverse effects. The most common adverse effect of acarbose is abdominal discomfort associated with flatulence and diarrhoea. These symptoms usually improve with continued treatment but can be minimised by starting with a low dose and titrating slowly.

Systemic adverse effects are rare but high doses have been associated with idiosyncratic elevations of serum hepatic transaminase levels. Patients titrated to the maximum dose of 200 mg three times daily should be closely monitored, preferably at monthly intervals for the first 6 months. If elevated transaminase levels are observed, reduction in dose or withdrawal of therapy should be considered.

Role of acarbose. Acarbose is a therapeutic option in type 2 patients inadequately controlled by diet alone, or by diet and other oral hypoglycaemic agents. However, the gastro-intestinal side effects do limit the use of acarbose in clinical practice.

Dipeptidyl peptidase-4 inhibitors

The DPP-4 inhibitors are a new class of drugs that work on the incretin system. They are also commonly referred to as the 'gliptins'.

Mode of action. DPP-4 inhibitors block the normal inactivation of incretins (glucagon like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]). Incretins play a role in increasing endogenous insulin in response to a high glucose load, that is, post-prandially. They also reduce the amount of glucose produced by the liver when glucose levels are sufficiently high. By blocking DPP-4, these drugs prolong incretin activity and inhibit glucagon release. This in turn causes a decrease in blood glucose and an increase in insulin secretion.

Pharmacokinetics. DPP-4 inhibitors are predominantly renally excreted. However, there is also a degree of hepatic metabolism involved in the elimination process, which varies with each drug. Sitagliptin is mainly excreted as unchanged drug in the urine, with a small metabolic contribution from the liver via the cytochrome P450 system. The kidney is thought to be mainly responsible for metabolic hydrolysis of vildagliptin to an inactive compound. Although saxagliptin is mainly eliminated renally, some hepatic biotransformation does occur via the cytochrome P450 system (CYP3A4/5), which results in a metabolite with half the potency of the parent compound. The pharmacokinetic parameters of the DPP-4 inhibitors are detailed in Table 44.4.

Adverse effects. All three DPP-4 inhibitors have been linked to gastro-intestinal side effects and upper respiratory tract infection. DPP-4 inhibitors do not cause hypoglycaemia, but they have the potential to cause hypoglycaemia when prescribed with other agents that can produce this effect. Vildagliptin has been associated with rare reports of liver dysfunction. Therefore, it is recommended liver function tests are performed prior to starting treatment, at 3-monthly intervals for the first year and then periodically thereafter.

Drug interactions. DPP-4 inhibitors have a low potential for interaction with other medicines. However, as both sitagliptin and saxagliptin are metabolised by cytochrome P450 3A4/5 (and CYP2C8 for sitagliptin), they have the potential to interact with potent inducers or inhibitors of these enzyme. In practice, few drugs have been formally assessed. Therefore, general advice is to monitor blood glucose levels carefully if one of these drugs is co-prescribed with sitagliptin or saxagliptin.

Role of dipeptidyl peptidase-4 inhibitors. DPP-4 inhibitors are licensed for use as dual therapy with metformin, a sulphonylurea or a thiazolidinedione. Sitagliptin is also licensed as both mono- and triple therapy with metformin and a sulphonlyurea or a thiazolidinedione. Similar to the thiazolidinediones, it is recommended that a DPP-4 inhibitor is used as third-line therapy typically in those who still do not have adequate control or cannot tolerate treatment with metformin and/or a sulphonylurea. DPP-4 inhibitors are also useful if further weight gain is likely. However, if insulin resistance is a key factor, then treating with a thiazolidinedione may be a better choice.

Incretin mimetics

The incretin mimetics, as the name suggests, mimic the effects of incretins. The two currently licensed in the UK, exenatide and liraglutide, are only available as subcutaneously injectable

products. Incretin mimetics have both been demonstrated to cause weight loss, which is a particularly beneficial effect in many patients with type 2 diabetes.

Mode of action. The incretin mimetics bind to and activate the glucagon-like peptide-1 (GLP-1) receptor, hence increasing insulin secretion, suppressing glucagon secretion, increasing satiety and slowing gastric emptying. All of these effects help to lower blood glucose levels.

Pharmacokinetics. Incretin mimetics have a longer duration of action than endogenous GLP-1. Exenatide is eliminated primarily by renal clearance. However, the specific organ responsible for liraglutide elimination has not been identified. Table 44.4 details additional pharmacokinetic parameters of the incretin mimetics.

Adverse effects. Both incretin mimetics have been associated with nausea, and other gastro-intestinal disturbances. However, once therapy has been established, the incidence of these side effects decreases. Acute pancreatitis has also been rarely reported. For this reason, both patients and their carers should be advised of the signs and symptoms of this complication and advised to stop taking the drug and seek medical attention immediately if they occur. Since the incretin mimetics cause glucose-dependent insulin release, hypoglycaemia is uncommon and in most cases can be attributed to other agents taken concurrently

Drug interactions. The potential for drug interactions with the incretin mimetics is low. However, as they can cause a delay in gastric emptying, they may influence the absorption of other medicines administered at the same time. For this reason, it is advised that any narrow therapeutic index drugs taken concomitantly are monitored carefully. Also, if other oral medicines are being taken where the threshold concentration is important (e.g. antibiotics), it is advised that these should be taken at least 1 h before exenatide. This may be assumed for liraglutide, although this is not specifically stated in the summary of product characteristics.

Role of incretin mimetics. It is recommended that exenatide be added to metformin and a sulphonylurea as third-line therapy (as an alternative to insulin, thiazolidinediones or DPP-4 inhibitors) for patients who have either a BMI of ≥35 kg/m^2, are of European decent (adjustments to this threshold may be made for other ethnic groups at greater risk of cardiac disease) and have other medical problems associated with increased body weight. Alternatively, exenatide may be used in patients with a BMI <35 kg/m^2 who are not able to take insulin, for example, for occupational reasons, or who have other conditions that would benefit from weight loss. Treatment should only be continued if there has been an HbA_{1c} reduction of at least 1% and a weight loss of at least 3% from starting treatment, over a 6-month period.

Insulin therapy in type 2 diabetes

The younger age of onset of type 2 diabetes and tighter glycaemic targets mean that the majority of patients with type 2 diabetes progress to insulin therapy, since recent evidence confirms that long-term glycaemic improvement reduces the risk of both microvascular (Holman et al., 2008) and macrovascular (Turnbull et al., 2009) complications.

It is currently common practice to introduce insulin to an oral medication schedule, although if hypoglycaemia becomes a problem, then the oral medications may be reduced or stopped. A number of different insulin regimens for use in patients with type 2 diabetes are available, the most common of which include once-daily basal insulin, twice-daily biphasic (pre-mixed) insulin, or prandial insulin, using a rapid/short-acting insulin with meals. Until recently, there have not been any trial data to determine which insulin regimen is most effective in controlling blood glucose levels and minimising hypoglycaemia in patients with type 2 diabetes. However, recent work suggests that patients who have basal insulin or prandial insulin added to their oral therapy have better HbA_{1c} control than those who receive biphasic insulin. In addition, the basal insulin regimen is associated with fewer hypoglycaemic episodes and less weight gain than the other two regimens (Holman et al., 2009). Basal insulin should be titrated to achieve normal fasting glucose levels, and the patient may be taught this self-titration protocol (Davies et al., 2005).

In a lean patient (BMI <25 kg/m^2), significant insulin deficiency is more likely and therefore from the outset of insulin treatment either a basal-bolus or twice-daily regimen may be preferred.

In type 2 patients who require temporary insulin during intercurrent illness, a soluble preparation such as Humulin S or Human Actrapid can be given two or three times daily with a small dose of isophane insulin at bedtime to control blood glucose quickly and eliminate symptoms. The dose is selected initially according to the patient's previous insulin requirements, if any, and adjusted according to four times daily blood glucose measurements.

Treating hypertension

The co-existence of hypertension and diabetes dramatically increases the risk of microvascular and macrovascular complications. Most important is the increased risk of cardiovascular disease. Tight control of blood pressure may be a more effective method of preventing complications in patients with type 2 diabetes than tight glycaemic control. It is recommended that, for patients with type 2 diabetes, the target blood pressure should be <140/80 mmHg, or for those with pre-existing kidney, eye or cerebrovascular damage the target should be reduced to <130/80 (National Institute for Health and Clinical Excellence, 2009). First-line blood-pressure-lowering therapy should be a once-daily, generically prescribed angiotensin-converting enzyme (ACE) inhibitor. Exceptions to this are people of African-Caribbean descent, in whom first-line therapy should be an ACE inhibitor plus either a diuretic or a generic calcium-channel blocker.

In young patients with type 1 diabetes, the blood pressure target is <135/80 mmHg. However, if there is abnormal albumin excretion (renal disease) or two features of the metabolic syndrome are present, then the blood pressure target should be lowered to 130/80 mmHg with maximal doses of either an ACE inhibitor or ARB as first-line therapy.

Treating obesity

Obesity is a significant risk factor in the development of type 2 diabetes. Evidence suggests that for each kilogram increase in body weight, the risk of diabetes increases by 4.5%. It is estimated that almost one-fifth of the population has a BMI of over 30 kg/m^2 and is therefore obese.

Treatment of obesity may require modification of lifestyle (diet and exercise regimens) to reduce calorie intake and increase calorie utilisation, pharmacological intervention and/or surgery. Currently orlistat, a lipase inhibitor, is the only drug available on prescription for the treating of obesity. Orlistat can also be purchased in community pharmacies as a branded over-the-counter product. Both sibutramine and rimonabant were withdrawn because of unwanted side effects.

Orlistat is licensed for use with a 'mildly hypocalorific diet' to treat obese people (BMI >30 kg/m^2) or overweight patients with a BMI >28 kg/m^2 and associated risk factors. It should be discontinued after 12 weeks if a 5% weight reduction since the start of treatment has not been achieved. Orlistat increases the amount of faecal fat excretion but is associated with a number of gastro-intestinal side effects such as oily leakage from the rectum, flatulence, faecal urgency and incontinence. A greater reduction in the incidence of type 2 diabetes has been observed in patients treated with both orlistat and lifestyle modification (Torgerson et al., 2004).

Over recent years, the use of bariatric surgery has increased in popularity, which is another treatment option for those who are seriously struggling with their weight with a BMI over 35–40 kg/m^2, who have other conditions caused by being overweight such as diabetes.

Patient care

Patient education

Patient involvement is paramount for the successful care of diabetes. This is highlighted in the national service standards for diabetes (Department of Health, 2002) which state that all patients, and carers, where appropriate, will be encouraged to develop a partnership with their clinicians to enable them to manage their diabetes and maintain a healthy lifestyle, often through shared care plans. Structured education for patients with type 2 diabetes is important and should be offered to every patient and/or their carer around the time of diagnosis. It is considered to be an integral part of diabetes care (National Institute for Health and Clinical Excellence, 2009).

Education will depend upon the individual patient and the availability of local resources. Individual tuition is preferable in the early stages after diagnosis and is usually delivered by a diabetes specialist nurse. The educational aspect of care is a gradual and ongoing process. At a later stage, group education can be effective and many patients appreciate and find support in meeting others who have the same disease. Many such programmes are multidisciplinary and involve doctors, nurses, dieticians, pharmacists and chiropodists. It is essential to involve the patient's family and carers in the educational process. Patients can also obtain support and information from specialist organisations such as Diabetes UK (available at www.diabetes.org.uk/home.htm).

Patients require education and information about many subjects, ranging from general lifestyle advice through to knowledge about the medicines they are prescribed (Box 44.4).

Advice about the use of over-the-counter medications, diet, foot care products and diabetic food products is frequently requested.

Annual review

People with diabetes should attend their hospital clinic or primary care practice (if this service is offered locally) for an annual review to screen for diabetic complications. Monitoring and optimising glycaemic control are also undertaken although this should be done on a more regular basis, as should review of patients with known complications. The annual review is increasingly taking place in primary care, with referral to secondary care if required. The typical assessments undertaken at an annual review are described in Box 44.5.

Box 44.4 Patient education in diabetes

1. The disease
   - Signs and symptoms
2. Hyperglycaemia
   - Signs, symptoms and treatments
3. Hypoglycaemia
   - Signs, symptoms and treatments
4. Exercise
   - Benefits and effect on blood glucose control
5. Diet
6. Insulin therapy
   - Injection technique
   - Types of insulin
   - Onset and peak actions
   - Storage
   - Stability
7. Urine testing
   - Glucose
   - Ketones
8. Home blood glucose testing
   - Technique
   - Interpretation
9. Oral hypoglycaemic agents
   - Mode of action
   - Dosing
   - Need for multiple therapies
10. Foot care
11. Management during illness
12. Cardiovascular risk factors
    - Smoking
    - Hypertension
    - Obesity
    - Hyperlipidaemia
13. Regular medical and ophthalmological examinations

Box 44.5 Annual review for diabetes

Routine assessment
Capillary blood glucose level
Weight, body mass index and waist circumference
Blood pressure
Urinalysis for glucose, protein and ketones
Foot assessment

Laboratory investigations
Fasting lipid profile
HbA_{1c}
U&E, creatinine
Liver function tests
Urine specimen for albumin:creatinine ratio (ACR)

Referral, if appropriate
Retinopathy screening (should be done annually)
Dietician
Podiatry
Exercise programme
Smoking cessation programme

Glycaemic management targets

The theoretical ideal for all patients with diabetes is to achieve normoglycaemia. As this is not always possible, the aim is to achieve the best possible control compatible with an acceptable lifestyle for the patient. In some patients, this may mean only symptomatic control, in others this may be tight control. In making this decision, the following factors should be considered: the patient's age, motivation, intelligence, understanding, likely adherence, co-existing diseases, ability to recognise hypoglycaemia, duration of their diabetes and the presence/absence/severity of diabetic complications.

Targets for pre-meal blood glucose of between 4 and 7 mmol/L and post-meal values of <10 mmol/L may be set for most patients, provided there is no significant hypoglycaemia risk. An optimal HbA_{1c} target of 6.5% for most of those with type 2 diabetes has been suggested (National Institute for Health and Clinical Excellence, 2009). However, it is recommended that targets should be individualised and that for some a higher target would be more appropriate especially if there is a risk of hypoglycaemia at the lower target. For those with type 1 diabetes, the recommended target is less than 7.5% (National Institute for Health and Clinical Excellence, 2004).

The diabetes treatment goals in older people may be different and more conservative than in younger adults. For example, some elderly patients may have poor vision and limited manual dexterity, which may or may not be linked to a degree of cognitive impairment. Others may have multiple pathology and take a number of other medications. Therefore, the goals of therapy need to be both individual and realistic. In some people, they will involve only the optimisation of body weight, control of symptoms and avoidance of hypoglycaemia which has an increased risk of severe brain damage and may occur without the usual warning signs in the elderly. In others, reasonably tight control may be appropriate. There is, therefore, a difficult balance between the use of aggressive treatment with its associated risk of hypoglycaemia and the benefits of reducing complications to maintain an acceptable quality of life. Box 44.6 sets out some of the common therapeutic problems in diabetes.

Box 44.6 Common therapeutic problems in diabetes

- Achieving normoglycaemia or HbA_{1c} targets
- Achieving an acceptable balance between improving glycaemic control and minimising episodes of hypoglycaemia
- Achieving adequate control in type 2 diabetes with diet alone, especially in patients who are overweight
- Drug-related weight gain, notably with insulin and sulphonylureas
- Achieving blood pressure targets in patients with co-existing hypertension
- Ensuring adherence as drug regimens become complex, requiring multiple drug therapies
- Making insulin therapy acceptable to patients with type 2 diabetes, inadequately controlled with oral therapies

Monitoring glycaemic control

Clinic monitoring

There are several ways in which glycaemic control can be monitored in primary and secondary care. Estimates of average control are often useful. Glycation of minor haemoglobin components occurs in the blood, with the extent depending on both the amount of glucose present and the duration of exposure of the haemoglobin to glucose. Estimates of glycated haemoglobin (HbA_{1c}) provide an index of average diabetes control over the preceding 2–3 months, that is, the lifespan of a red blood cell. HbA_{1c} can be measured at any time, the patient does not need to be fasted, and levels are not normally affected by acute changes in therapy, diet or exercise. However, they may be lower in those with reduced red cell lifespan, for example, pregnancy or advanced renal failure. Serum fructosamine represents the glycation of all serum proteins and gives information about control over the preceding 3 weeks. As albumin is the major serum protein, hypoalbuminaemia may affect fructosamine levels. However, HbA_{1c} is the preferred marker for average glycaemic control.

Home monitoring

Type 1 diabetes. All patients treated with insulin should be offered home blood glucose monitoring (HBGM). Capillary blood is applied to a reagent strip which has been impregnated with enzymes, for example, glucose oxidase. Some home blood glucose monitoring methods require visual comparison of colour changes which correspond to various blood glucose concentrations. More commonly, meters may be used to give readings and are more convenient for people who are colour blind or who have poor eyesight. Home blood glucose monitoring enables patients and carers to make a direct assessment

of the effect of changes in medicines, dietary habits, exercise and patterns of illness. It has the additional benefit that it can detect hypoglycaemia and, unlike urine testing in which glycosuria may only be detected some time after changes in blood glucose have occurred, it enables more accurate calculations of insulin doses.

Patients with type 1, who are by definition ketosis prone, should also know how and when to test their urine for ketones. This test need not be carried out as part of routine monitoring but is essential at times of intercurrent illness, especially when the blood glucose is ≥17 mmol/L.

Type 2 diabetes. Many people with type 2 diabetes are treated with diet alone or with oral hypoglycaemic agents, and unless they have problems with hypoglycaemia, urine glucose monitoring should be adequate. This is a simple non-invasive test that can detect hyperglycaemia but not hypoglycaemia. Home blood glucose monitoring is used by some patients with type 2, particularly if control is poor, if they are undergoing medication dose titration, if they are being treated with insulin or if they are prone to hypoglycaemia. It is also recommended that blood glucose monitoring be undertaken before driving and at times of intercurrent illness, when blood glucose levels may be particularly erratic.

Regardless of whether individuals with type 1 or type 2 diabetes are using home blood glucose monitoring or urine testing, it is important they are educated about what to do with the results; otherwise, there is little point in testing.

Case studies

Case 44.1

Mrs TM is a 36-year-old married lady who has type 1 diabetes. She undertook a home pregnancy test because she was feeling particularly nauseated in the mornings and her period was late. The test was positive confirming that she was pregnant. However, at 8 weeks, she experienced vaginal bleeding and abdominal pain. She attended the Accident & Emergency department, where a miscarriage was confirmed. Upon questioning, it was discovered that she had been taking folic acid 400 µcg daily for the previous 6 months but had not received any pre-conception diabetes care. Her most recent HbA_{1c} was 7.3% (56 mmol/mol). Her regular medications are ramipril 10 mg daily, simvastatin 40 mg daily, insulin glargine at night and insulin aspart three times daily with meals.

Questions

1. Why should women of childbearing age be offered advice about pregnancy?
2. What blood glucose targets should Mrs TM have been advised to aim for before and after conceiving?
3. Was she taking appropriate dietary supplements prior to conception?
4. What advice should she be given with respect to her regular medication?

Answers

1. Mrs TM should have been offered preconception advice prior to becoming pregnant because glucose control needs to be optimal to reduce the risks of miscarriage, congenital malformation, stillbirth and neonatal death associated with diabetes in early pregnancy. Preconception advice should also include information for the patient on how diabetes affects pregnancy and how pregnancy affects diabetes, what dietary supplements to take and advice on diabetes-related medicines that are unsafe to take during pregnancy.
2. Mrs TM should aim for an HbA_{1c} target of below 6.1% (43 mmol/mol) before conceiving. During pregnancy, she should aim for fasting blood glucose levels of 3.5–5.9 mmol/L and 1-h post-prandial levels of below 7.8 mmol/L.
3. Mrs TM was taking the appropriate dietary supplement; however, the recommended dose for women with diabetes is 5 mg daily, rather than 400 µcg daily. The 5-mg strength tablets are available on prescription.
4. Mrs TM should have been advised to stop her ramipril and simvastatin since both have been associated with an increased risk of birth defects.

Case 44.2

Mr LG is a 47-year-old man with type 2 diabetes. He has recently had basal insulin (insulin detemir) added into his other diabetes medicines: metformin modified release 1 g twice a day and gliclazide 80 mg twice a day. He complains of waking with a headache and feeling 'groggy' and unrested in the morning. His recent blood glucose readings have generally been very good although his before breakfast readings are 10–13 mmol/L. He is worried because he is feeling worse since he started insulin, even though his blood glucose levels are much improved. He has made an appointment with his primary care doctor. His primary care doctor suspects nocturnal hypoglycaemia may be causing his recent symptoms.

Questions

1. What is nocturnal hypoglycaemia?
2. Why might nocturnal hypoglycaemia cause raised blood glucose levels in the mornings?
3. How can the diagnosis of nocturnal hypoglycaemia be confirmed?
4. How should it be treated?

Answers

1. Nocturnal hypoglycaemia is a low blood glucose reading that occurs during the night. Definitions vary but it is generally accepted that a reading of less than 3.5 mmol/L is 'hypoglycaemia'. The normal symptoms of hypoglycaemia may be missed if the patient does not wake. However, signs noticed (often by partners) might include restlessness, sweating and nightmares. Symptoms experienced by the patient in the mornings commonly include headache, lethargy and raised blood glucose levels.
2. Nocturnal hypoglycaemia may be caused by a rebound rise in blood glucose levels due to the 'somogyi effect'. This is the effect of the counter-regulatory hormones, glucagon, cortisol, adrenaline (epinephrine) and growth hormone, which all increase glucose in response to low levels.

3. Commonly, nocturnal hypoglycaemia can be confirmed by undertaking a blood glucose reading in the early hours of the morning, that is, between 2 and 4 am. This may require the patient to set their alarm to be woken at this time.
4. Nocturnal hypoglycaemia once confirmed may be treated by either having a bed-time snack, or by reducing the dose of night-time insulin. In the case of Mr LG, stopping his sulphonylurea may also help resolve the problem. Care must be taken when interpreting raised blood glucose levels in the morning, since the obvious intervention would be to increase the dose of night-time insulin. However when nocturnal hypoglycaemia is the cause, increasing the insulin dose would only make the problem worse and more dangerous for the patient.

Case 44.3

Mr PT is a 69-year-old man with longstanding type 2 diabetes. He has recently noticed that his right shoe has been rubbing his foot, which he finds confusing since he has been wearing these shoes for 6 months with no problems. His whole left foot now looks red and swollen and when Mr PT inspected it closely, he noticed that there was a weeping sore. However, his foot is not painful, so he does not feel too concerned.

Questions

1. What is the most likely reason that Mr PT did not feel any pain associated with the sore?
2. Why might Mr PT's shoe suddenly have started to rub his foot?
3. Should he be more concerned?

Answers

1. Mr PT has probably developed sensory neuropathy in his feet. This usually begins with the loss of the sensation of vibration and then may progressively lead onto the loss of sensation altogether.
2. The shape of the feet of people with diabetes has been observed to change over time. This may be due to the development of neuropathy which can weaken muscles causing alterations to the shape of the arch of the foot and toes. In this case, we know that Mr PT has sensory neuropathy since he is unable to feel the pain of the weeping sore. It is likely that Mr PT may also have motor neuropathy.
3. Mr PT should be concerned because his lack of sensation does not indicate that the foot injury is not serious. He is at risk of developing an infected ulcer and needs prompt treatment to prevent the problem from becoming severe. If he does not seek treatment, he may even risk losing his foot through amputation.

Case 44.4

Miss IL is a 17-year-old teenager with recently diagnosed type 1 diabetes. She has been admitted to hospital with diabetic ketoacidosis (DKA), which was precipitated by a diarrhoea and vomiting bug. As she was vomiting she was not eating, and hence she temporarily stopped injecting her insulin. She is normally well controlled on a basal bolus insulin regimen comprising insulin glargine (Lantus) at night and insulin glulisine (Apidra) three times daily with meals.

Questions

1. Why was it a mistake for Miss IL not to inject her insulin whilst she was not feeling well enough to eat?
2. What advice should patients on insulin be given regarding glucose management when they are feeling unwell and not able to eat normally?
3. What are the initial management priorities for patients admitted with diabetic ketoacidosis?
4. What is the correct way for subcutaneous insulin to be re-introduced after a patient has been on a continuous intravenous insulin infusion?

Answers

1. This is a common misunderstanding amongst patients and sometimes even health care professionals. When a person is unwell, their basal insulin requirements can often increase, despite not eating. This is because of the stress involved and the increase in the production of counter-regulatory hormones which increase glucose levels.
2. Patients should be counselled on what are commonly referred to as 'sick day rules' and should be given contact numbers for advice if they are unclear or struggling with management. Generally patients need to increase the frequency of glucose monitoring to 4-hourly or more and test urine for ketones on a regular basis. Carbohydrate intake should be maintained as much as possible using sugary drinks or fruit juice, soups, jelly or snack foods if they are having difficulty in eating. Fluid intake is important and patients should be advised to have a glass of water every hour, aiming for 3 L in 24 h. If the blood glucose level is less than 12 mmol/L and ketone result is negative-small, patients should continue their normal insulin dose. If the blood glucose level is between 12 and 18 mmol/L and the ketone result is negative-small, the patient should re-test within 4 h or at the next meal and add 4 extra units of insulin to doses of up to 20 units and 8 extra units to doses greater than 20 units. If the blood glucose level is more than 18 mmol/L and ketones are moderate or large, patients should take 50% extra insulin. If blood glucose is more than 20 mmol/L and ketones are moderate or large, the dose of insulin should be doubled. If the patient is vomiting and blood glucose levels are over 16 mmol/L, then medical help should be sought, especially if there is no improvement after the second test or the next insulin injection.
3. Intravenous sodium chloride 0.9% should be started as soon as possible. A fixed rate intravenous insulin infusion should then be started. Current recommendations are to begin at a rate of 0.1 units/kg. Regular hourly monitoring of blood glucose and ketones should be undertaken and 2-hourly monitoring of serum potassium for the first 6 h.
4. When the patient is biochemically stable, they may be converted back to subcutaneous insulin. The current national guidelines from the Joint British Societies Inpatient Care Group (2010) recommend that long-acting subcutaneous insulin analogues are continued throughout treatment of diabetic ketoacidosis in order to prevent rebound hyperglycaemia when the intravenous infusion is stopped. Therefore, Miss IL's glargine should have been continued. Her rapid-acting insulin (Apidra®) should be re-introduced at the next meal and the intravenous insulin infusion should be stopped 30 min afterwards.

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Menstrual cycle disorders 45

K. Marshall and S. Calvert

Key points

- Girls can begin experiencing menstrual disorders once ovulatory cycles are established.
- Up to 95% of women experience changes premenstrually, but severe premenstrual syndrome is more common in the 30–40 year age group.
- The aetiology of premenstrual syndrome is multifactorial, the symptomatology complex and treatment options diverse.
- It has been estimated that 50–80% of women of child-bearing age will suffer from dysmenorrhoea at some time.
- Treatment options vary according to the type of dysmenorrhoea (primary or secondary) but include non-steroidal anti-inflammatory drugs, combined oral contraceptive pills, and progestogen-only preparations.
- Menorrhagia (excessive menstrual blood loss) affects up to 30% of menstruating women. The management of the condition depends upon the cause and can be either surgical or medical.
- Endometriosis (the presence of extrauterine endometrial tissue) can give rise to an array of symptoms including subfertility. Treatment may be designed to improve fertility and manage symptoms. Medical and surgical treatments are available.

Once a girl reaches puberty, various physiological events occur, leading to the onset of menstruation, or the menarche. The average age of the menarche has decreased to around 12.5 years and a halt in this trend towards earlier menarche is not evident. This decline has been attributed to an improvement in nutrition and overall health. Body weight is linked to menarchal age and it is possible that as body fat increases so does serum leptin (hormone which influences calorie intake) which in turn may increase the pulsatile release of gonadotrophin-releasing hormone (GnRH).

Menstruation is an event that occurs relatively late in puberty and 95% of girls reach the menarche between the ages of 11 and 15 years. One UK study has shown that one girl in eight begins to menstruate whilst still at primary school. Even before the first ovulatory cycle has taken place, childhood ovarian activity will have gradually increased the production of oestrogen, leading to the development of the secondary sexual characteristics. These events are probably initiated by the central nervous system (CNS) which ultimately triggers the necessary gonadal changes that will eventually lead to the establishment of the menstrual cycle. It may take up to 2 years for the hypothalamic–pituitary–gonadal axis to mature and for regular ovulation to take place. In girls who only start to menstruate when they are older, it may take even longer. This should be considered when taking a patient's medical history.

Menstruation itself occurs as a result of cyclic hormonal variations (Fig. 45.1). During the first half or follicular phase of the menstrual cycle, the endometrium thickens under the influence of increasing levels of oestrogen (most notably estradiol, which at the peak of its preovulatory surge reaches around 2000 pmol/L) secreted from the developing ovarian follicles. Once the serum oestrogen level has surpassed a critical point it triggers, by positive feedback, the anterior pituitary to release, about 24 h later, a surge of luteinising hormone (LH; up to 50 iu/L) and after 30–36 h, ovulation follows.

After ovulation, which occurs around day 14 of a 28-day menstrual cycle, and as the luteal phase progresses, the endometrium begins to respond to increasing levels of progesterone. Both progesterone and oestrogen are secreted from the corpus luteum which is formed from the remains of the ovarian follicle after ovulation. The lifespan of the corpus luteum is remarkably constant and lasts between 12 and 14 days; hence, the length of the second half or the luteal phase of the menstrual cycle is between 12 and 14 days. Between days 18 and 22 of a 28-day cycle, both sex steroids peak, with levels of progesterone reaching around 30 nmol/L. As progesterone has a thermogenic effect upon the hypothalamus, basal body temperature

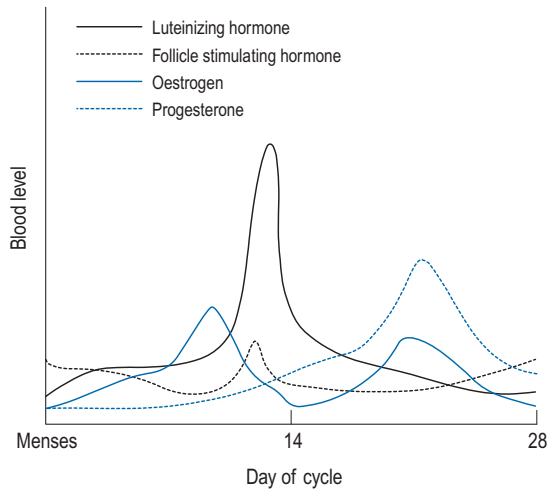


Fig. 45.1 The hormonal events that occur during the menstrual cycle in women.

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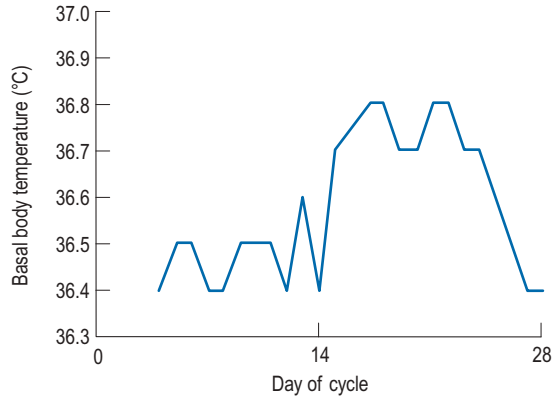


Fig. 45.2 Typical temperature chart from a 28-day ovulatory menstrual cycle.

increases by about 1 °C in the second half of an ovulatory cycle (Fig. 45.2). Most ovulatory cycles range from 21 to 34 days.

These synchronised changes mean that about a week after ovulation, the endometrium is prepared for implantation, providing fertilisation has taken place. If conception does not occur, then luteolysis begins and steroid levels fall. This means that the endometrium cannot be maintained, there is a loss of stromal fluid, leucocyte infiltration begins and there is intraglandular extravasation of blood. Finally, endometrial blood flow is reduced and this leads to necrosis and sloughing, that is menstruation. Initially, the blood vessels that remain intact after sloughing are sealed by fibrin and platelet plugs; subsequent haemostasis is probably achieved as a result of vasoconstriction of the remaining basal arteries. Nitric oxide may be involved in the initiation and maintenance of menstrual bleeding by promoting vasodilation and inhibiting platelet aggregation. The myometrium is the muscular layers of the uterus that contract spontaneously throughout the menstrual cycle, the frequency of these contractions being influenced by the hormonal milieu. The myometrium is also more active during menstruation. The average blood loss per period is between 30 and 40 mL.

There is evidence which suggests a physiological and pathological role for the local hormones, known as prostaglandins, in the process of menstruation. Prostaglandins are 20-carbon oxygenated, polyunsaturated bioactive lipids, which are cyclooxygenase-derived products of arachidonic acid. Indeed, both the myometrium and the endometrium are capable of synthesising and responding to prostaglandins. A potential role for another family of autocoids, the leukotrienes, in the regulation of uterine function remains uncertain, although it is known that leukotrienes can also be synthesised from arachidonic acid by lipoxygenase enzymes (Fig. 45.3).

Disorders associated with menstruation are a major medical and social problem for women which also impact upon their families.

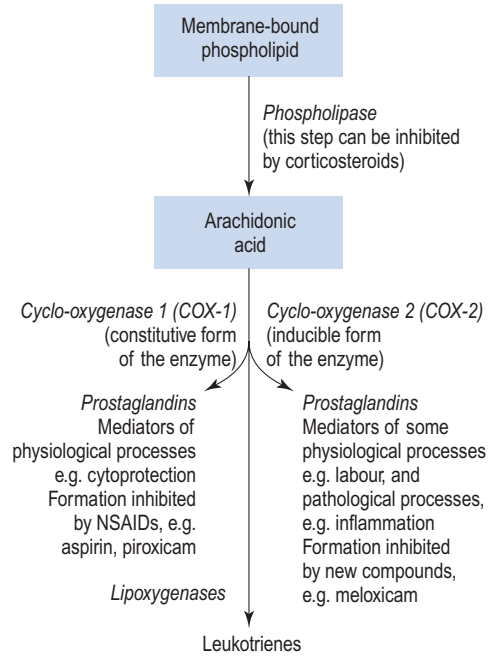


Fig. 45.3 Eicosanoid biosynthesis and inhibition.

Premenstrual syndrome (PMS)

PMS encompasses both mood changes and physical symptoms. Symptoms may start up to 14 days before menstruation, although more usually they begin just a few days before and disappear at the onset of, or shortly after, menstruation. However, for some women, the beginning of menstruation may not signal the complete resolution of symptoms. Numerous studies have demonstrated that this condition can cause substantial impairment of normal daily activity, including reduced occupational activity and significant levels of work absenteeism. Severity varies from cycle to cycle and may be influenced by other life factors such as stress and tiredness. The most severe form of PMS may be referred to as premenstrual dysphoric disorder (PMDD) as defined by the Modified Diagnostic and Statistical Manual of Mental Disorders appendix IV, or DSM-IV (American Psychiatric Association, 2000) and for which the criteria are set out in Box 45.1. Other bodies (American College of Obstetricians and Gynecologists, 2000) have published diagnostic criteria for PMS (Box 45.2). There is considerable overlap between PMS and PMDD.

Epidemiology

Up to 95% of menstruating women experience some changes premenstrually. Clinically relevant PMS occurs in about 15–20% of these women and PMDD has an estimated incidence of 3–8%. It has been estimated that PMS may account for over 17 million disability-adjusted life years (DALYS) in the European Union. PMS affects young and older women alike and does not appear to be influenced by parity. Severe PMS is more common in the 30–40 year age range, and married women with young children commonly seek help. Certain events may be linked with the onset of PMS, including childbirth, cessation of oral contraceptive use (incidence of reported PMS is lower in pill users), sterilisation, hysterectomy or even increasing age.

Box 45.1 Summary of DSM-IV diagnostic criteria for premenstrual dysphoric disorder (PMDD)

One-year duration of symptoms which are present for the majority of cycles (occur luteal/remit follicular)

Five of the following symptoms (with at least one of these*) must occur during the week before menses and remit within days of menses.

- Irritability*
- Depressed mood or hopelessness*
- Affective lability* (sudden mood swings)
- Tension or anxiety*
- Decreased interest in activities
- Change in sleep patterns
- Difficulty concentrating
- Feeling out of control or overwhelmed
- Lack of energy
- Other physical symptoms, for example, breast tenderness, bloating
- Change in appetite, for example, food cravings

Seriously interferes with work, social activities, relationships

Not an exacerbation of another disorder

Confirmed by prospective daily ratings during at least two consecutive symptomatic cycles

Box 45.2 Diagnostic criteria for premenstrual syndrome (PMS)

Patient reports ≥1 of the following affective and somatic symptoms during the 5 days before menses in each of three prior menstrual cycles:

Affective	Somatic
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

Symptoms relieved within 4 days of menses onset without recurrence until at least cycle day 13

Symptoms present in absence of any pharmacological therapy, hormone ingestion, or drug or alcohol abuse

Symptoms occur reproducibly during two cycles of prospective recording

Patient suffers from identifiable dysfunction in social or economic performance

PMS may be exacerbated by other stresses, typically those associated with family life. Women with a body mass index over 30 are more likely to suffer from PMS. There is also some evidence that crimes, accidents, examination failure, absenteeism and marital disturbances may be more common premenstrually.

Aetiology

PMS is not seen before puberty, during pregnancy or in postmenopausal women, and therefore, the ovarian hormones have been implicated. The mineralocorticoids, prolactin, androgens, prostaglandins, endorphins, nutritional factors (e.g. pyridoxine, calcium and essential fatty acids) and hypoglycaemia may be involved. In addition, changes in CNS function have been implicated as cerebral blood flow in the temporal lobes is decreased premenstrually in PMS sufferers, and noradrenergic cyclicity is disrupted. As symptoms vary so much from cycle to cycle, and from individual to individual, it is likely that different aetiological factors apply to different women, all of which may be affected by extenuating emotional circumstances. There is some evidence that predisposition to PMDD may be familial.

Hormones

The cyclicity of PMS suggests an ovarian involvement. This is substantiated by the fact that it is still experienced after hysterectomy if the ovaries are left intact and that it disappears during pregnancy and after the menopause. One theory attributes PMS to luteal phase progesterone deficiency leading to a progesterone/estradiol imbalance, but there is no direct clinical evidence to support this in terms of serum progesterone levels. However, the problem could lie at the cellular level, that is, a paucity of functional steroid receptors leading to differential sensitivity to hormones. Alternatively, it could be a central control defect, as ovarian suppression by GnRH analogues can alleviate symptoms in some women; however, the use of these drugs is generally not recommended because of their unwanted effects associated with production of a hypooestrogenic state.

The central actions of the sex steroids or their neuroactive metabolites are important. Research into the complex relationship between the steroids and the CNS is ongoing, and progressing with the advent of new tools such as the progesterone receptor modulators. Estradiol increases neuronal excitability possibly via increasing the activity of glutamate (an important excitatory neurotransmitter). Progesterone, and its metabolites, can bind to the γ-aminobutyric acid A ($GABA_A$) receptor, and this interaction would induce an effect similar to that evoked by benzodiazepines. The mineralocorticoid, aldosterone, may be associated with the increase in fluid retention as serum levels of this hormone are elevated in the luteal phase. However, no significant difference in blood levels of this mineralocorticoid has been found between PMS sufferers and non-sufferers. In contrast, one study has found that baseline levels of cortisol were elevated during the luteal phase in PMS sufferers.

Prolactin is secreted from the decidual cells at the end of the luteal phase of the menstrual cycle as well as from the anterior pituitary. This hormone has a direct effect upon breast tissue and hence may be associated with breast tenderness. Prolactin is also associated with stress and has an indirect relationship with dopamine metabolism and release in the CNS. It promotes sodium, potassium and water retention.

However, there are no consistent differences in hormone blood levels of prolactin between PMS sufferers and non-sufferers. Again, the differences could lie at the receptor level. Local hormones such as the prostaglandins may also be implicated in the aetiology of PMS as synthesis of these autocoids can be affected by the sex hormones as well as substrate availability. Prostaglandin imbalance is implicated in PMS as increased synthesis of certain prostaglandins, for example, PGE_2, have antidiuretic and central sedative effects as well as promoting capillary permeability and vasodilation. Deficiencies of others, for example, PGE_1, which can attenuate some of the actions of prolactin, may also contribute to the syndrome.

Vitamins and minerals

Pyridoxine phosphate is a co-factor in a number of enzyme reactions, particularly those leading to production of dopamine and serotonin (5-hydroxytryptamine). It has been suggested that disturbances of the oestrogen/progesterone balance could cause a relative deficiency of pyridoxine, and supplementation with this vitamin appears to ease the depression sometimes associated with the oral contraceptive pill. Decreased dopamine levels would tend to increase serum prolactin, and decreased serotonin levels could be a factor in emotional disturbances, particularly depression. There is some evidence that premenstrual mood changes are linked to cycle-related alterations in serotonergic activity within the CNS and, therefore, serotonin may be important in the pathogenesis of PMS. There are also data to suggest that a variety of nutrients may play a role in the aetiology of PMS, specifically calcium and vitamin D. Further hydroxylation of 25-hydroxyvitamin D_3 ($25(OH)D_3$) takes place in target tissues which include the breast and the endometrium. In the Nurses' Health Study II (NHSII), high total vitamin D intake lowered risk of PMS by almost a third (Bertone-Johnson et al., 2005). Oestrogen influences calcium metabolism by affecting intestinal absorption, and parathyroid gene expression and secretion, so triggering fluctuations throughout the menstrual cycle. Disruption of calcium homeostasis has been associated with affective disorders.

Essential fatty acids

Essential fatty acids, such as γ-linolenic (or gamolenic acid/GLA), provide a substrate for prostaglandin synthesis. γ-Linolenic is converted into dihomo-γ-linolenic acid, which forms the starting point for the synthesis of prostaglandins of the 1 series (e.g. PGE_1). It has been suggested that women with PMS are abnormally sensitive to normal levels of prolactin and that PGE_1 is able to attenuate the biological effects of this hormone. Hence, if there is a γ-linolenic deficiency, then there is less substrate for PGE_1 synthesis. Therefore, the effect of prolactin with respect to breast tenderness, fluid retention and mood disturbances may be exaggerated. Numerous other dietary factors may also be involved, including excess saturated fats and cholesterol, moderate-to-high alcohol consumption, zinc and magnesium deficiencies, diabetes, ageing and viral infections, all of which hinder the conversion of cis-linolenic acid to γ-linolenic. Pyridoxine, ascorbic acid and niacin also increase conversion of γ-linolenic to PGE_1, while there is some evidence to suggest that linolenic acid metabolite levels are reduced in women with PMS.

Psychological factors

PMS may not be wholly explicable in pathophysiological terms, but it should not be regarded as a psychosomatic disorder as there is no simple relationship between its existence, severity and personality. It is not strictly confined to particular types of women, although there is no doubt that PMS interacts with many aspects of life, especially difficult or stressful times. The latter has been termed the 'vulnerability factor' which, although not a function of the menstrual cycle, can affect the way a woman reacts.

Symptoms

Symptoms occur 1–14 days before menstruation begins and disappear at the onset or shortly after menstruation begins. For the rest of the cycle, the woman feels well. Symptoms are cyclical, although they may not be experienced every cycle, and can be either physical and/or psychological (see Boxes 45.1. and 45.2 for symptomatology). The lives of the 5% or so of women who are severely affected may be completely disrupted in the second half of the menstrual cycle. The symptoms of PMS tend to decrease as a woman gets closer to the menopause as her ovulatory cycles become less frequent.

Management

The first step in the management of PMS is recognition of the problem and realisation that many other women also suffer. Keeping a menstrual diary is useful and will establish any link between symptoms and menstruation, and this will provide a cornerstone for diagnosis. After a few months, it will allow the patient to make predictions and help her deal with changes when they arrive. The effectiveness of medical intervention depends upon which symptoms are being experienced, underlining the importance of a menstrual diary and experimentation. In terms of treatment, self-help and perseverance will be required in the management of PMS. The wide variety of symptoms may require exploring a number of treatment options before optimal relief can be achieved.

Non-pharmacological strategies

Maintenance of good general health is important, especially with respect to diet and possible deficiencies. Dietary modifications that may be helpful include restricting caffeine and alcohol intake. Smoking can also exacerbate symptoms. Exercise may help, as may learning simple relaxation techniques. If fluid retention is a problem, then reducing fluid and salt intake may be of value. Increasing the intake of natural diuretics such as prunes, figs, celery, cucumber, parsley and foods high in potassium such as bananas, oranges, dried fruits, nuts, soya beans

and tomatoes may all be useful. Hypoglycaemia may also be involved in premenstrual tiredness, so eating small protein-rich meals more frequently may help.

Results from clinical trials involving pyridoxine (vitamin B_6) have shown conflicting results. However, some women do respond to pyridoxine and show improvement, particularly with respect to mood change, breast discomfort and headache. A typical dosage regimen would be 50 mg twice daily after meals or 100 mg after breakfast. The dose should not exceed 100 mg a day. Gastric upset and headaches have been reported at doses greater than 200 mg. High doses over long periods have also been associated with peripheral neuropathies. Pyridoxine should be commenced 3 days before symptom onset and continued for 2 days after menstruation has started.

Calcium supplementation has shown some activity in reducing emotional, behavioural and physical symptoms. Likewise, there is limited evidence that supplementation with γ-linolenic acid, found in evening primrose oil, gives relief from physical symptoms, especially breast tenderness.

Pharmacological management

Progestogens. Synthetic progestogens, in preparations such as Cyclogest® and Duphaston®, have been used in the past. However, because of the lack of convincing trial evidence and the risk of side effects, the use of progestogens is no longer recommended. Possible side effects include weight gain, nausea, breast discomfort, breakthrough bleeding and changes in cycle length. Problems arise because some synthetic progestogens, especially 19-nor compounds such as norethisterone and levonorgestrel, also display some affinity for glucocorticoid, mineralocorticoid and androgen receptors. The specificity of these synthetic agents is influenced by the substituents present on the steroid nucleus, particularly at C13. For example, the third-generation progestogens that have an ethyl group at C13 (gestodene, desogestrel and norgestimate) have the least androgenic activity of all the 19-nor compounds but are still orally active.

Combined oral contraceptives (COC). Some women are helped by the COC pill because it prevents ovulation from taking place. However, the use of exogenous oestrogen may be contraindicated because it can increase the risk of venous thromboembolism. This occurs because oestrogen decreases blood levels of the potent natural anticoagulant antithrombin III and at the same time increases serum levels of some clotting factors. Women with other risk factors for thromboembolic disease should also avoid this form of therapy. The incidence of venous thromboembolism in healthy, nonpregnant women who are not taking an oral contraceptive is about five to ten cases per 100,000 women per year. For those using COCs containing second-generation progestogens, for example, levonorgestrel, this incidence is about 15 per 100,000 women per year of use. Some studies have reported a greater risk of venous thromboembolism in women using preparations containing the third-generation progestogens desogestrel and gestodene. The incidence in these women is about 25 per 100,000 women per year of use. However, it should be noted that the absolute risk of venous thromboembolism in women using COCs containing these third-generation progestogens remains very small and well below the venous thromboembolism risk associated with pregnancy.

It is thought that use of third-generation progestogens is associated with increased resistance to the anticoagulant action of activated protein C. Oral contraceptive treatment diminishes the efficacy with which activated protein C down regulates *in vitro* thrombin formation. This is known as activated protein C resistance and is more pronounced in women using the COC pills containing desogestrel than in women using those containing levonorgestrel. However, it has also been recognised that women who do react to third-generation progestogens with venous thromboembolism may be revealing a latent thrombophilia. There are several conditions, congenital or acquired, that can cause thrombophilic alterations. A genetic factor known as factor V Leiden mutation is the most common inherited cause of thrombophilia, and this mutation results in resistance to the effects of activated protein C. Carriers of this mutation have more than a 30-fold increase in risk of thrombotic complications during oral contraceptive use, although this has been disputed (Farmer et al., 2000) because no increase in risk of venous thromboembolism was found with the third-generation progestogens. In conclusion, if there is a history of thromboembolic disease at a young age in the immediate family, then disturbances of the coagulation system must be ruled out.

The combination of ethinylestradiol with drospirenone is also available as an oral contraceptive and appears to be useful in the management of PMS. Drospirenone is a derivative of spironolactone, with affinity for progesterone receptors, but it also acts as a mineralocorticoid antagonist. This progestogen, therefore, alleviates some of the salt-retaining effects of the ethinylestradiol.

Bromocriptine. Bromocriptine stimulates central dopamine receptors and thus inhibits the release of prolactin. It may be useful for breast tenderness and occasionally has beneficial effects upon fluid retention and mood changes. It should be used in small doses, for example, 1–1.25 mg at bedtime with food, to avoid the side effects of nausea and faintness due to hypotension. The dose can be slowly increased to 2.5 mg twice a day if required. It is advised that ergot-derived dopamine receptor agonists, such as bromocriptine, have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions (Anon, 2002). Excessive daytime sleepiness and sudden onset of sleep can also occur with dopaminergic drugs.

Danazol. Danazol is a synthetic steroid derived from ethisterone. It is weakly androgenic and has been described as an attenuated androgen. Danazol interacts with androgen receptors, but it also has some affinity for the progesterone receptor. It inhibits the pulsatile release of gonadotrophins from the anterior pituitary and so abolishes cyclical ovarian activity, leading to amenorrhoea in the majority of women and a subsequent fall in serum oestrogen levels. However, because of the high incidence of side effects, it tends to be used as a last resort for relief of severe mastalgia and mood changes. These side effects relate to the androgenicity of the compound and include nausea, giddiness, muscular pain, weight gain, acne and virilisation. These can be minimised by using low doses of 200 mg a day.

Gonadotrophin-releasing hormone analogues. GnRH analogues, sometimes referred to as gonadorelin analogues, are useful for managing the physical symptoms, but are less effective with respect to emotional symptoms. These agents inhibit the hypothalamic–pituitary–gonadal axis. However, they can only be used for short periods of time, no more than 6 months, because they induce a hypo-oestrogenic state, and therefore bone loss becomes significant after 6 months' treatment. Should a patient respond well to GnRH analogues for PMS following hysterectomy, because of underlying pelvic pathology, bilateral oophorectomy may also be of benefit.

Prostaglandin synthesis inhibitors. Improvements in tension, irritability, depression, headache and general aches and pains can be seen in some women who take prostaglandin synthesis inhibitors. Most of the information available centres upon the use of mefenamic acid at doses of 250 mg three times a day 12 days before a period is due, increasing to 500 mg three times a day 9 days before the period and continuing until the third day of menstruation. Other inhibitors of prostaglandin synthesis are likely to be just as effective and may be associated with fewer side effects. Some experimental evidence, however, suggests that, in addition to being a cyclo-oxygenase inhibitor, mefenamic acid also has activity as an antagonist at prostaglandin E receptors, and therefore this may be useful if heavy menstrual bleeding is also a problem. For optimum effectiveness, this form of therapy should be started 24 h before the onset of symptoms. However, this starting point may be difficult to predict for women with irregular cycles.

Antidepressants. The selective serotonin reuptake inhibitors (SSRIs) are becoming more popular in the treatment of PMS-related depression because they are effective and well tolerated (Brown et al., 2009). Several randomised controlled trials using fluoxetine, sertraline, citalopram, fluvoxamine or paroxetine concluded that SSRIs are an effective first-line therapy for severe PMS and the side effects at low doses are generally acceptable. Two studies also found that not only do SSRIs improve behavioural symptoms, but some improvement in physical symptoms was also noted. Common side effects experienced include headache, nervousness, drowsiness and fatigue, sexual dysfunction and gastro-intestinal disturbances. Other agents such as tricyclic antidepressants and anxiolytics such as buspirone have been used. However, they appear to improve fewer PMS symptoms than the SSRIs.

St John's Wort has been used to reduce the severity of PMS, but the available evidence is limited.

Dysmenorrhoea

Dysmenorrhoea is usually subdivided into primary and secondary dysmenorrhoea. The former may also be referred to as spasmodic dysmenorrhoea, which is a uterine problem and is predominantly a complaint of young women. Secondary dysmenorrhoea is so called because it occurs secondary to some underlying pelvic pathology such as endometriosis or pelvic inflammatory disease (PID).

Epidemiology

The estimates vary but epidemiological studies suggest that between 50% and 80% of women will suffer from dysmenorrhoea at some time during their reproductive life, and up to 15% of these women will be seriously debilitated by the condition, with social and economic consequences. In the USA, it has been estimated that dysmenorrhoea accounts for the loss of 600 million working hours which equates to >2 billion dollars. Women in Western countries now have fewer pregnancies and this may be a contributory factor in the increasing prevalence of dysmenorrhoea.

Primary dysmenorrhoea

Aetiology and symptoms

The incidence of primary dysmenorrhoea peaks in women in their late teens and early 20s, the pain coinciding with establishment of ovulatory cycles. A typical sufferer will usually complain of lower abdominal pain (cramping), which may radiate down into the thighs, and backache. Some women also suffer gastro-intestinal symptoms (nausea, vomiting, diarrhoea), headaches and faintness. Symptoms are intense on the first day of menses but rarely continue beyond day 1 or 2 of the cycle. Factors that appear to increase the severity include young age at menarche, extended duration of menstrual flow (pain can be most severe when the flow is lighter), smoking and parity (the prevalence and severity of dysmenorrhoea is decreased in parous women). Other factors such as weight, length of menstrual cycle or frequency of physical exercise do not influence the condition.

In terms of aetiology, studies carried out in the 1950s and 1960s first drew attention to the possible role of the prostaglandins. This was followed by many *in vivo* studies which showed that women suffering from primary dysmenorrhoea do have greater concentrations of prostaglandins, predominantly $PGF_{2\alpha}$, and to some extent PGE_2, in their menstrual fluid compared with matched control subjects. Such a prostaglandin imbalance would favour increased myometrial contractility. The effects of the prostaglandins on human myometrium are now well documented, and increased biosynthesis of prostaglandins may also account for the gastro-intestinal problems encountered by some sufferers. A role for the prostaglandins is substantiated by the fact that women whose diet contains more omega-3 fatty acids tend to suffer less. When eicosapentaenoic acid (EPA) is the substrate for prostaglandin biosynthesis, prostaglandins of the three series are produced (e.g. PGE_3 and TXA_3). Such local hormones are less potent stimulators of the myometrium and less effective vasoconstrictors. Other potential mediators are the endothelins, vasoactive peptides produced in the endometrium that may play a role in the local regulation of prostaglandin synthesis, and vasopressin, a posterior pituitary hormone that stimulates uterine activity and decreases uterine blood flow. The smaller branches of the uterine arteries are very sensitive to the vasoconstrictor actions of these mediators, and it is these resistance vessels that are important in the control of uterine blood flow. The interrelationship between blood flow and myometrial activity is summarised in Fig. 45.4.

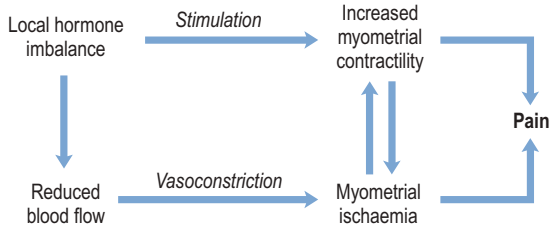


Fig. 45.4 The interactive role of myometrial stimulants and vasoconstrictive agents in the pathway leading to pain in dysmenorrhoea.

Measurements of intrauterine pressure and myometrial activity have been made for research purposes, but there are no simple objective measurements for dysmenorrhoea.

Secondary dysmenorrhoea

Aetiology and symptoms

Secondary dysmenorrhoea tends to afflict women in their 30s and 40s, and usually occurs as a consequence of some other pelvic pathology such as endometriosis or pelvic inflammation. In terms of symptoms, it differs from primary dysmenorrhoea in that the pain may actually start before menstruation begins, continue for the duration of menses and be associated with abdominal bloating, backache and a general feeling of 'heaviness' in the pelvic area. The intrauterine contraceptive device may also exacerbate menstrual pain, since it causes localised inflammation that triggers the release of prostaglandins. The prostaglandins may also be implicated in the chain of events that lead to pain associated with secondary dysmenorrhoea. For example, if the cause is endometriosis, in which endometrial tissue is found outside the uterine cavity, then this extrauterine tissue can also synthesise prostaglandins, which may in turn disrupt normal uterine function.

Treatment

In terms of analgesia, the most rational choice would be a non-steroidal anti-inflammatory drug (NSAID) (Zahradnik et al., 2010), as these compounds decrease prostaglandin biosynthesis by inhibiting cyclo-oxygenase. Differences in anti-inflammatory activity between different NSAIDs are small. However, there is considerable variation in individual patient tolerance and response, and a lack of response to one particular agent does not mean that a patient would not respond to a different NSAID.

Mefenamic acid is frequently used to manage pain due to dysmenorrhoea. As previously stated, this compound not only inhibits prostaglandin production but also appears to possess some prostaglandin E receptor blocking activity which may serve to augment its effect. However, these preparations are not suitable for all women and some, about 30% of women, will not respond. There is substantive evidence (Marjoribanks et al., 2010) that NSAIDs are effective in the treatment of dysmenorrhoea and are more effective than paracetamol. However, there is insufficient evidence regarding the comparative efficacy of individual agents in terms of superiority of analgesia or side-effect profile.

The lack of an effect with an NSAID may be explained by pathway diversion, since the arachidonic acid that was to be converted to a prostaglandin via the action of cyclo-oxygenase can be utilised by an alternative biosynthetic route, leading to increased formation of leukotrienes. Alternatively, the second cyclo-oxygenase enzyme (COX-2), which is generally induced under pathological conditions, may be involved. Many of the currently available NSAIDs are relatively poor inhibitors of COX-2, and if some of the prostaglandins in these uterine disorders are produced via the action of this form of cyclo-oxygenase, then it is not surprising that the NSAIDs are not 100% effective. Celecoxib and etoricoxib have been shown to be effective, although none is currently licensed for use in dysmenorrhoea.

A small study has investigated the use of the leukotriene receptor antagonist montelukast (Singulair®) in the treatment of dysmenorrhoea (Fujiwara et al., 2010). The results suggest blockade of leukotriene receptors alleviate pain and reduce NSAID usage, and this appears to be most effective in women without endometriosis.

It has been estimated that approximately 50% of primary dysmenorrhoea sufferers will gain relief from taking the oral contraceptive pill, although, as this is a condition afflicting young girls, there may be attitudinal problems to the use of these products either in the patient or her parents. The oral contraceptive pill inhibits ovulation and thereby prevents increased luteal phase prostaglandin synthesis and so decreases uterine contractility. However, not all women are suitable candidates for COC use because of the potential problems associated with exogenous oestrogen. Contraindications include high blood pressure, obesity and a significant personal or family history of venous thromboembolism. Progestogenic preparations (e.g. dydrogesterone 10 mg twice daily from day 5 to 25 of cycle, norethisterone 5 mg three times daily from day 5 to 24 of the cycle) or progestogen-only pills may be useful if they inhibit ovulation. For pain relief, there appears to be no significant difference between the various formulations. Antispasmodics such as hyoscine butylbromide and propantheline bromide have a very limited role in the treatment of dysmenorrhoea, not least because of their poor oral bioavailability. Related compounds such as atropine also have negligible effects upon the human uterus. A summary of the treatment options for dysmenorrhoea is presented in Table 45.1. Future therapy may involve use of vasopressin antagonists. Clinical trials have shown these compounds to be effective and well tolerated and they do not affect bleeding patterns.

For secondary dysmenorrhoea, the best treatment lies in finding the underlying cause and then taking an appropriate therapeutic route. For example, if some form of PID is diagnosed that can be attributed to a causative organism, then antimicrobial therapy is appropriate. PID is most commonly caused by the presence of a sexually transmitted infection. The most frequent causative organisms are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. In addition, any procedure that may compromise the mucus barrier of the cervix, for example, insertion of an intrauterine device, may also

Table 45.1 Summary of treatment options for dysmenorrhoea

Drug	Side effects
NSAIDs	Gastric irritation, which can be minimised by taking with or after food or selecting an agent with less gastrotoxicity, for example, ibuprofen. Hypersensitivity reactions, particularly bronchospasm. Headache, dizziness, vertigo, hearing problems (e.g. tinnitus) and haematuria. NSAIDs may adversely affect renal function and provoke acute renal failure
Combined oral contraceptives	Many side effects are dose related and so the development of the ultra-low-dose preparations (i.e. those containing 20 µcg ethinylestradiol) is beneficial. An alternative to the oral preparations is the low-dose transdermal combined contraceptive which releases 20 µcg ethinylestradiol and 150 µcg of norelgestromin (active metabolite of the third-generation progestogen, norgestimate). The most serious potential adverse effect is the increased risk of thromboembolism due to a decrease in circulating levels of antithrombin III while increasing serum levels of some clotting factors. This risk increases with age and smoking. Analysis of current data suggests that the risk of breast cancer is not increased for most women who use the combined oral contraceptive for the major portion of their reproductive years. Use of the combined oral contraceptive also conveys several health benefits besides being an effective contraceptive. The progestogenic side effects are discussed as follows
Progestogen-only preparations	Use of these agents may cause menstrual disturbances, for example, breakthrough bleeding. Other adverse effects relate to the selectivity of the synthetic hormone, for example, norethisterone is a first-generation progestogen and has some affinity for steroid receptors other than progesterone and so possesses androgenic, oestrogenic and antioestrogenic activity. The third-generation progestogens (gestodene, norgestimate and desogestrel) have the least androgenic activity. This should be advantageous as it is the androgenicity of the compounds that correlates with the decrease in high-density lipoproteins

increase the risk of contracting PID. Treatment of endometriosis will often reduce symptoms of dysmenorrhoea. Surgical treatment for secondary dysmenorrhoea such as hysterectomy is also possible for those women who do not want to become pregnant.

Non-pharmacological management options have recently been reviewed and include high-frequency transcutaneous nerve stimulation (TENS) and acupuncture (Proctor et al., 2002). Both of these therapies showed some potential benefit. There is limited evidence to support the use of uterine nerve ablation and presacral neurectomy, to interrupt the sensory nerve fibres near the cervix blocking the pain pathway. Dietary therapies such as vitamin and mineral supplementation have also been investigated. One study identified that vitamin B_1 100 mg daily may be effective in relieving pain (Proctor et al., 2002). Magnesium supplementation also shows promising results. Unfortunately, evidence is still lacking to support use of other herbal and dietary therapies, for example, omega-3 fatty acids. Some Chinese herbal medicines have shown interesting results but trial quality is poor.

Menorrhagia

Blood loss is considered to be excessive if it exceeds 80 mL per period, although both women themselves and clinicians find it difficult to objectively quantify blood loss. In practice, it is defined by the woman's subjective assessment of blood loss. Any change in menstruation, whether real or perceived, may be disturbing with respect to social, occupational or sexual activities and can lead to other problems including depression and concern about an undiagnosed problem such as cancer. Physically excessive blood loss will precipitate iron deficiency anaemia (haemoglobin <12 g/dL) which, if left undiagnosed and untreated, will compound the problems outlined earlier.

If a patient has any intermenstrual or postcoital bleeding, then referral to a gynaecologist for endometrial biopsy is essential to exclude intrauterine pathology. Up-to-date cervical cytology is also required. It should also be noted that hormonal contraceptives may cause some irregular spotting or breakthrough bleeding, but this is generally a tolerance effect. Non-oral methods, particularly implants, depots and intrauterine systems decrease bleeding with continued use (see later). WHO recommends a 90-day reference period for reporting vaginal bleeding.

Epidemiology

In the UK, about 30% of women complain of heavy menstrual bleeding, and about 1 in 20 women aged 25–44 years consult their primary care doctor about this problem. Historically, once referred to a gynaecologist, 60% of women could expect to have a hysterectomy within 5 years. Recent changes in the management of women with menorrhagia and new treatment options, particularly endometrial ablations and the levonorgestrel intrauterine contraceptive devices (LNG-IUS), have significantly reduced hysterectomy rates for menorrhagia to a third of the number 10 years ago.

Aetiology and investigation

The aetiology of menorrhagia can be divided into three categories: underlying pelvic pathology, systemic disease and dysfunctional uterine bleeding (Box 45.3). The typical symptoms suggestive of underlying pelvic pathology are presented in Box 45.4. Pelvic pathologies associated with menorrhagia

Box 45.3 Causes of menorrhagia (percentage frequency)
Dysfunctional uterine bleeding (60%), that is cause is unknown
Other gynaecological causes (30%): Uterine or ovarian tumours Endometriosis Pelvic inflammatory disease Intrauterine contraceptive devices Early pregnancy complications
Endocrine and haematological causes (<5%) Thyroid disorders, for example hypothyroidism Platelet problems and clotting abnormalities

Box 45.4 Symptoms suggestive of underlying pelvic pathology
Irregular bleeding
Sudden change in blood loss
Intermenstrual bleeding
Postcoital bleeding
Dyspareunia
Pelvic pain
Premenstrual pain

include myomas (fibroids, common benign tumours of the myometrium), endometriosis, adenomyosis (penetration of endometrial tissue into the myometrium), endometrial polyps, polycystic ovarian disease and endometrial carcinoma. Although endometrial cancer is more typically seen in postmenopausal women, approximately 50% of those patients diagnosed with it premenopausally will have associated menorrhagia. Systemic diseases from which menorrhagia may stem include hypothyroidism, disorders involving the coagulation system such as elevated endometrial levels of plasminogen activator and systemic lupus erythematosus. Very few women fall into this group. About 60% of menorrhagia sufferers have no underlying systemic or pelvic pathology and have ovulatory cycles. These patients are said to have dysfunctional uterine bleeding and local uterine mechanisms appear to be important in the control of menstrual blood loss. Occasionally, cycles may be anovulatory, with heavy blood loss because the endometrium has become hyperplastic under the influence of oestrogen. In addition, use of an intrauterine contraceptive device may also increase menstrual blood loss.

Prostaglandins appear to play a role in the aforementioned local mechanisms and have been implicated in menorrhagia. Studies have suggested an association between the type and quantity of endometrial prostaglandin synthesis and the degree of menstrual blood loss. In the mid-1970s, it was discovered that women with heavy periods had raised endometrial levels of $PGF_2\alpha$ and PGE_2 and that blood loss could be reduced by the use of drugs inhibiting prostaglandin formation. More studies suggested that, in menorrhagic women, there is a shift towards increased biosynthesis of PGE_2, which is known to dilate uterine vasculature and/or increase the number of membrane receptors for this prostanoid. The availability of arachidonic acid, a substrate for prostaglandin synthesis, is also greater in women with menorrhagia. Levels of the vasodilators or their metabolites, PGI_2 and nitric oxide (NO), are also increased in the menstrual blood collected from women with excessive blood loss. It has been suggested that menorrhagia is an angiogenesis-related disease associated with changes in the pattern of vascular fragility involving the upregulation of various vascular endothelial growth factors.

Excessive menstrual blood loss is the most common cause of iron deficiency anaemia in women of reproductive age. In an otherwise healthy, well-nourished woman, it has been estimated that menstrual blood loss would have to exceed 120 mL to precipitate iron deficiency anaemia. Objective measurement of menstrual blood loss is difficult, so measurement of full blood count (including red blood cell indices and serum ferritin levels), and in particular, haemoglobin concentration, gives some indication of blood loss. Thyroid function should also be assessed. If fibroids are suspected, then pelvic ultrasound may be required. Endometrial biopsy is needed if there is an associated irregularity of menstruation or if intermenstrual or postcoital bleeding is present. In the case of regular menses, however, investigation of the uterine cavity would usually only be required in women over the age of 35 years or if medical treatment fails to alleviate symptoms. Young women presenting with dysfunctional uterine bleeding may have underlying coagulopathies such as von Willebrand's disease or Christmas disease, which should be excluded.

Treatment

The management of menorrhagia depends upon the cause of the condition and a woman's desire to conceive. Treatment can be either surgical or medical (Table 45.2). The effectiveness of drug therapy is obviously influenced by the accuracy of the diagnosis. Drug treatment is also influenced by a woman's contraceptive needs; for example, COCs can reduce menstrual blood loss by up to 50%, but in women over 35 years of age who smoke, this form of therapy would need careful consideration. Low-dose luteal phase progestogens are no longer recommended for treatment of heavy but regular periods as they increase menstrual blood loss in this situation. However, they may be of value in women with an irregular cycle. Long-term, long-acting progestogens, however, may render a woman amenorrhoeic. Other hormonally based therapies include the GnRH analogues, although their propensity to induce a hypo-oestrogenic state with long-term use may be problematic (a 6-month course would reduce trabecular bone density by 5–6%). Danazol can reduce menstrual blood loss but its use is generally prohibited by its side-effect profile. However, in 2009, a local vaginal treatment of 200 mg a day was investigated in 55 women (Luisi et al., 2009). Results showed danazol to be effective in reducing blood loss and few

Table 45.2 Summary of drug treatment options for menorrhagia

Drug	Comments
Combined oral contraceptive	See Table 45.1. These preparations are taken for 21 days with a 7-day pill-free (or placebo) period to allow for a withdrawal bleed
Progestogen-only preparations	See Table 45.1. Compounds such as norethisterone can be used, for example, 5 mg three times daily or 10 mg twice daily for the latter half of the cycle. Ten days of therapy should be sufficient from day 15 of the cycle in ovulatory cycles. However, if the cycles are anovulatory, then a minimum of 12 days' therapy is more appropriate. Progestogens for 12 days are also required to prevent endometrial hyperplasia in peri- and postmenopausal women taking oestrogen. When progestogens such as norethisterone are used, the dosage required is higher than that used in the combined oral contraceptive pill, and the adverse effects associated with the synthetic progestogens, particularly the 19-nortestosterone derivatives, may be more pronounced
Intrauterine progestogen-only contraceptive	The levonorgestrel-releasing intrauterine device (LNG-IUS) typically releases 20 µcg of levonorgestrel/24 h. Unlike non-medicated IUCDs, which may increase menstrual blood loss, this device appears to reduce it, as a result of the local endometrial actions of the progestogen. The device also offers contraceptive cover without many of the side effects associated with the non-medicated IUCDs. Progestogen-related side effects should be minimised because of the low dose of levonorgestrel employed. Initially, bleeding patterns may be disrupted, but menstrual blood loss should become lighter within three menstrual cycles
Danazol	Danazol suppress the pituitary–ovarian axis. Side effects include amenorrhoea, hot flushes, sweating, changes in libido, vaginitis and emotional lability. Danazol also causes androgenic side effects such as acne, oily skin and hair, hirsutism, oedema, weight gain, voice deepening and decreasing breast size. Danazol has to be taken daily
GnRH analogues (gonadorelin)	After an initial period of stimulation, these agents suppress the pituitary–ovarian axis. As result of inducing a hypo-oestrogenic state, these compounds should only be used for 6 months because they may decrease trabecular bone density
NSAIDs	These agents only need to be taken for the first 3–4 days of menses
Tranexamic acid	This drug appears well tolerated, but can produce dose-related gastro-intestinal disturbances. Patients who may be predisposed to thrombosis are at risk if given antifibrinolytic therapy. This compound is usually only taken for the first 3 days of menses

IUCDs, intrauterine contraceptive devices; GnRH, gonadotrophin-releasing hormone.

adverse effects were reported. A trial of ormeloxifene, a selective estrogen receptor modulator (similar to raloxifene), 60 mg twice weekly has been used successfully to reduce blood loss with relatively few side effects (Kriplani et al., 2009).

Prostaglandins have been implicated in the aetiology of several forms of menorrhagia. Therefore, NSAIDs may be of use in some patients, especially if there is pain associated with menstruation. The NSAIDs appear to be most effective in women with the heaviest blood loss, for example, mefenamic acid 500 mg three times daily from day 1 until heavy flow ceases.

Women with menorrhagia have greater endometrial fibrinolytic activity, hence the use of antifibrinolytic drugs, which are plasminogen activator inhibitors. Tranexamic acid became available for purchase over the counter in UK pharmacies in 2010 as Cyklo-F®. This can be sold to women aged 18–45 years old with a history of regular heavy menstrual bleeding over several consecutive menstrual cycles. Tranexamic acid reduces menstrual blood loss by up to 50% (Lethaby et al., 2000), the recommended dose being 1 g three times daily starting on the first day of menses for up to 4 days. Agents such as tranexamic acid carry a risk of unwanted thrombogenesis, but this does not appear to be translated into practice as increased numbers of deep vein thromboses. This class of drugs decreases menstrual blood loss better than NSAIDs and oral luteal phase progestogen (Lethaby et al., 2005). However, tranexamic acid should be stopped if it has produced no benefit after three cycles.

The levonorgestrel intrauterine contraceptive devices (also known as intrauterine systems or LNG-IUS) can be left in place for up to 5 years following insertion. They reduce menstrual blood loss by up to 90% after 12 months of use. The levonorgestrel-releasing intrauterine system provides relief from dysmenorrhoea, effective contraception and long-term control of menorrhagia. A study showed that the levonorgestrel-releasing intrauterine device was the most cost-effective treatment followed by ablation surgery (Clegg et al., 2007). In addition, other slow-release progestogenic devices such as nesterone implants and vaginal rings also reduce menstrual blood loss and promote amenorrhoea.

Hysterectomy has been the traditional surgical treatment for menorrhagia, with either an abdominal or vaginal approach used (Marjoribanks et al., 2006). Newer alternatives to hysterectomy include endometrial ablation, which can be done by electrosurgical, laser, microwave or thermal techniques. Endometrial ablation is less invasive than hysterectomy, but recurrence of menorrhagia can occur and amenorrhoea cannot be guaranteed. There is evidence that pretreatment with a single dose of a GnRH agonist before the ablation procedure gives a better result. These preparations cause an initial stimulation of gonadotrophin release which then suppresses the hypothalamic–pituitary axis, producing a hypo-oestrogenic state. If circulating levels of oestrogen are low, then endometrial growth will not be stimulated; thus, it will be thinner, making the surgical endometrial destruction more effective. With GnRH pretreatment, modern techniques such as microwave ablation have achieved amenorrhoea rates of about 50% and patient satisfaction rates of 90%.

Endometriosis

Endometriosis is a condition in which endometrial tissue is found outside the uterus. These so-called ectopic endometrial foci have been found outside the reproductive tract in the gastro-intestinal tract, the urinary tract and even the lungs.

Aetiology

Aetiology remains unclear, although retrograde menstruation, when shed endometrial cells migrate up through the fallopian tubes, would appear to be involved. This may occur because abnormalities in uterine innervation cause disruption in the usual patterns of myometrial contractility with consequent loss of the usual fundocervical polarity. Endometriosis is found in women in whom the normal route for the menstrual flow is disrupted, such as when there is some genital tract abnormality. Women who have frequent and heavier periods also seem to be more likely to suffer from endometriosis. Familial predisposition may also be a factor and several gene polymorphisms have been identified.

Studies suggest that endometrium from endometriosis sufferers tends to be more invasive. This may reflect either biological or genetic differences in the peritoneal milieu and may be explained by the upregulation of certain types of metalloproteinase responsible for the degradation of basement membrane. Endometrial tissue from women with endometriosis has aromatase activity which can be stimulated by PGE_2. Therefore, ostensibly the endometriotic lesions have their own oestrogen supply as aromatase converts androgenic precursors into oestrogen and oestrogen stimulates biosynthesis of PGE_2; thus, the cycle is self-perpetuating. *In vitro* studies have shown that eutopic and ectopic endometrial explants have different lipidomic profiles in terms of their prostaglandin release and the myometrium from endometriosis suffers is more acontractile during menses. Pilot studies in the USA using aromatase inhibitors, such as anastrozole and letrozole, are ongoing.

Epidemiology

Endometriosis was previously considered to be a disease affecting women in their 30s onwards, but increasing use of laparoscopy has revealed that it can occur at any time throughout a woman's reproductive life. The condition is dependent upon oestrogen stimulation, and as such, it does not occur before the menarche or after the menopause. The exact incidence of the disease is unknown, but it is believed to be about 10% in the general female population of reproductive age. One study has found a positive correlation between a menarche before 13 years and increased risk of developing endometriosis.

Symptoms

Although not all women with endometriosis are symptomatic, the pelvis is the most commonly affected site. Consequently, most of the symptoms of endometriosis relate to this region. Symptoms take the form of dysmenorrhoea and pelvic pain. However, the severity of the pain does not necessarily reflect the extent of the disease because women with severe pain may have few lesions, and vice versa. Dyspareunia often with postcoital discomfort is also common. There may also be menstrual irregularities.

The link between endometriosis and infertility is recognised, but the mechanisms involved have not been established. If the ovaries or fallopian tubes themselves are directly affected by the endometriotic lesions, then fertility may be compromised by purely mechanical means. However, the situation is less clear when the endometriosis does not cause any anatomical distortions. In this case, some of the postulated causes of infertility associated with endometriosis include ovulation disorders such as luteinised unruptured follicle syndrome, anovulation, premature ovulation; hyperprolactinaemia; and changes in the peritoneal environment such as extrauterine endometrial material which, like normal endometrium, is subject to control by the ovarian steroids and like its uterine counterpart is also capable of producing prostaglandins. Prostaglandin levels, along with macrophage concentrations, are raised in the peritoneal fluid of women with endometriotic explants, and these may alter tubular and uterine motility within the abdomen.

Outside the reproductive tract, endometrial deposits can be found along the urinary and gastro-intestinal tracts. If the former is involved, then the patient may suffer from cyclical haematuria, dysuria or even ureteric obstruction. If there is gastro-intestinal tract involvement, then symptoms could include dyschezia, cyclical tenesmus and rectal bleeding or even obstruction. Very occasionally, the lesions are found at more distant sites such as the lungs, where they could cause cyclical haemoptysis. A reduction in bone mass in women with endometriosis has also been reported.

Treatment

The aims of treatment in endometriosis are to relieve symptoms and improve fertility if pregnancy is desired. Treatment can be either surgical or medical. Surgery is increasingly

performed laparoscopically and can be employed to restore normal pelvic anatomy, divide adhesions or ablate endometriotic tissue using either laser treatment or electrodiathermy. Medical treatment utilises the fact that endometriotic tissue is oestrogen dependent, and any drug therapy that will oppose the effects of oestrogen should, among other things, inhibit the growth of the endometriotic tissue. Hence, the choices of drug treatment are as follows.

- GnRH analogues such as buserelin, goserelin, leuprorelin and nafarelin. These initially stimulate the hypothalamic–pituitary–ovarian axis but thereafter induce a hypo-oestrogenic state by paradoxically inhibiting follicle-stimulating hormone (FSH) and LH release.
- Low-dose COC (20–30 µcg of ethinylestradiol) monophasic preparations have been found to be as effective as GnRH analogues, and they may slow down disease progression in young women and preserve future fertility.
- Compounds with androgenic activity such as danazol also inhibit pituitary gonadotrophin release by interfering with the negative feedback and cause atrophy of endometrial tissue.
- Progestogens such as dydrogesterone, medroxyprogesterone acetate and norethisterone initially cause decidualisation of the endometrial tissue followed by glandular atrophy.

None of the aforementioned drug therapies are free from side effects. Use of the GnRH analogues may evoke menopausal symptoms such as hot flushes, decreased libido, vaginal dryness (topical vaginal lubricants may be helpful), mood changes and headache. The problems associated with the hypo-oestrogenic state limit the long-term use of GnRH analogues. Although lipoprotein levels are not affected adversely, bone mass is, and this loss of bone density may not be entirely reversible after cessation of therapy. Various 'add-back' hormone replacement therapies have been successfully used to minimise bone demineralisation, for example, low-dose oestrogen/progestogen combinations used continuously. Such regimens protect against osteoporosis and other hypo-oestrogenic side effects without apparently affecting clinical efficacy. Pain associated with endometriosis was relieved similarly by gosarelin and a low-dose oral contraceptive (Prentice et al., 1999). However, side-effect profiles differed, for example, hot flushes and vaginal dryness with the former agent and headache and weight gain with the latter.

The androgenic compounds, because of their very nature, are associated with hirsutism, weight gain and acne. Side effects associated with synthetic progestogens relate again to androgenicity, although dydrogesterone is free from virilisation. However, using a levonorgestrel-releasing intrauterine device ensures the low dose of levonorgestrel is delivered locally and the more direct pelvic distribution may be useful in the management of endometriosis. Recent results suggest this device causes the downregulation of endometrial cell proliferation and increased apoptotic activity. Longer-term studies, over 5 years, need to be undertaken to determine how long this effect is maintained and also effectiveness on symptoms such as dyspareunia and dyschezia.

Researchers have also found that certain dietary changes may be beneficial and reduce symptoms. A decreased intake of glycaemic carbohydrates such as sugar, rice and potatoes in addition to reducing/eliminating caffeine and increasing the intake of omega-3 oils such as flax seed oil may also be helpful. In addition, one study found that women with endometriosis tended to have a lower body mass index than those without the condition.

Total pelvic clearance, including the removal of the ovaries, is practical in women who have completed their family. This tends to be a last resort treatment but it is usually effective. However, surgery may be difficult if multiple lesions are present. There is no evidence that hormonal suppression improves surgical outcome.

Neither surgical nor medical management is effective in all cases. Studies suggest that pain associated with endometriosis responds well to both surgical and medical treatment, but symptoms of recurrence occur in about 50% of patients within 5 years of stopping treatment. Fertility may be increased by the use of surgery to remove endometriotic foci causing anatomical distortion. The same benefit is not associated with medical treatment.

Case studies

Case 45.1

A 13-year-old girl is brought to her primary care doctor by her mother. She has been struggling with long, heavy periods for 6 months and as a result is missing time at school.

Questions

1. What non-hormonal treatment options would be considered?
2. What other treatments might be an option?

Answers

1. In young girls, it is worthwhile trying non-hormonal treatment options first as they will tend to have a lower side-effect profile than hormonal treatment. Tranexamic acid at a dose of 1 g three times a day should be taken while bleeding. This is a very simple and effective option with few side effects and a reported 50% reduction in menstrual blood loss. Another option would be to try a non-steroidal preparation such as mefanamic acid (500 mg three times daily from first day of bleeding until period ends), especially if associated dysmenorrhoea is a significant problem. Tranexamic acid and an NSAID can be taken together if required.
2. Cyclical norethisterone (5 mg three times daily from day 5 to day 25 of cycle) can be helpful if the periods are irregular, but it is not recommended for heavy regular periods. Progestogenic side effects such as nausea and bloating can limit use. The COC pill can be very effective at relieving menorrhagia and dysmenorrhoea, provided that there are no contraindications. Sometimes, parents can raise concerns about the use of a contraceptive agent, some parents perhaps believing that it may promote promiscuity.

Case 45.2

A 33-year-old woman has been diagnosed with endometriosis having presented with severe dysmenorrhoea. She has visited the gynaecology clinic to discuss treatment options but is very concerned about her fertility. She does not wish to conceive at the present time but would certainly plan to try for a baby in the next couple of years.

Questions

1. What effect does endometriosis and its treatment have on fertility?
2. What treatment options could be considered?

Answers

1. Severe endometriosis with significant distortion of the pelvic anatomy can cause tubal blockage and hence cause tubal factor infertility. Most patients will have much less severe endometriosis which, although not causing any anatomical abnormality, is associated with a reduction in fertility. Such couples tend to take longer to conceive perhaps because the endometrial deposits create an unfavourable milieu for the egg and sperm. Surgical treatment such as diathermy or laser destruction or excision of endometriotic deposits may improve fertility, although such surgery can be complicated. Medical treatments are not associated with an improvement in fertility rates as many treatment options are contraceptive in themselves and should not be used if women wish to try to conceive. In this situation, symptom control with analgesia may be the best option.
2. As this patient is not wishing to conceive, a trial of medical therapy should be considered. Surgery for endometriosis is a highly skilled procedure which has a significant risk of complications. Medical treatment options include GnRH analogues, the COC pill or a prolonged course of progestogens such as medroxyprogesterone acetate. All have different side effects and contraindications but are all equally effective at reducing symptoms of endometriosis. Currently, the most popular option is a 6-month course of a GnRH analogue which is generally well tolerated. Vasomotor symptoms can be treated with add-back hormone replacement therapy with a continuous combined preparation or tibolone. Treatment is limited to a 6-month course because of the bone loss associated with the GnRH-induced hypo-oestrogenism. The COC pill can be taken in a conventional way, but anecdotal experience supports tricycling, that is, taking 3 packets back to back and only having a withdrawal bleed after the third packet. Clearly, the usual contraindications to taking a COC pill apply. Progestogens are often poorly tolerated with side effects such as bloating and nausea.

Case 45.3

A 33-year-old with very heavy and prolonged periods presents to her primary care doctor requesting hysterectomy. Her mother had a hysterectomy at age 38 and this patient feels that it is her only option.

Questions

1. What treatment options would you offer this patient before considering hysterectomy?
2. What investigations are necessary?

Answers

1. Before considering treatment, the patient should have a pelvic examination, primarily to exclude large fibroids which are unlikely to respond to medical therapy. Current advice is to recommend a levonorgestrel-releasing intrauterine device as first line for heavy menstrual bleeding (NICE, 2007). If the patient declines this, other options would include tranexamic acid and/or a non-steroidal NSAID such as mefenamic acid taken at the onset of the period. The COC pill could be considered if not contraindicated. Cyclical norethisterone may be of benefit if the menstrual cycle is irregular. Hysterectomy should be reserved as the last option and if medical therapy fails. Consideration should be given to an endometrial ablative procedure before resorting to major surgery.
2. If pelvic examination is normal, the only investigation recommended for this lady is a full blood count to exclude anaemia. If examination suggests the possibility of a pelvic mass, an ultrasound scan should be organised. Further endometrium investigation, by hysteroscopy or endometrial biopsy, in women under 45 with heavy menstrual bleeding and no intermenstrual bleeding, is not indicated unless medical treatment options fail.

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46 Menopause

K. Marshall and S. Calvert

Key points

- Menopause is signalled by the last menstrual period; this cessation of menstruation results from a loss of ovarian follicular activity.
- The problems associated with menopause result from the ensuing loss of the female sex steroid oestrogen.
- On average, 35% of a woman's life is spent in a peri-menopausal or post-menopausal state.
- Declining oestrogen levels can give rise to vasomotor symptoms, localised atrophy of the genitalia, psychological problems, osteoporosis and coronary heart disease.
- In the UK, only about 50% of women seek help for their symptoms.
- The hormonal content of a particular hormone replacement therapy (HRT) regimen is important, as is the route of delivery, in determining the side effects observed.
- Contraindications to HRT include undiagnosed vaginal bleeding in post-menopausal women or the presence of an oestrogen-dependent tumour.
- For women with an intact uterus, hormone replacement regimens must include a progestogenic component to prevent overstimulation of the endometrium.
- Alternative options to traditional HRT regimens include the use of tibolone, raloxifene and the bisphosphonates.

Menopause

The UK, like many countries in the developed world, has an ageing population, life expectancy is increasing and women continue to live longer than men, whilst birth rates are declining. Currently, a woman can expect to live about 35% of her life in a post-menopausal state.

Menopause is signalled by a woman's last menstrual period and is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity. The occurrence of the last menstruation can only be diagnosed retrospectively and is usually taken as being final if it is followed by a 12-month bleed-free interval; such women are defined as being post-menopausal. The mean age of menopause in the UK is 51 years, and by the age of 54 years, around 80% of women will be post-menopausal. If menopause occurs before 40 years, it would be classed as a premature menopause. Many women will experience erratic periods before the final cessation due to inadequate ovarian oestrogen secretion; these women are described as being peri-menopausal. This transitional phase usually lasts around 4–5 years. The problems associated with menopause result from oestrogen deprivation. Hormone replacement therapy (HRT) reduces the effects of this deprivation and overcomes the associated symptoms.

Menopause is a natural event in the anatomical, physiological and psychological changes which form the female climacteric. Some women will go from the transition of being pre-menopausal to post-menopausal with no symptoms at all. Many will experience the symptoms associated with oestrogen lack, whether in the peri-menopausal or post-menopausal phase, which include:

- vasomotor symptoms
- localised atrophy of urogenital tissues
- osteoporosis
- psychological problems
- coronary heart disease.

Initially, the symptoms are more likely to include vasomotor symptoms such as hot flushes, night sweats and palpitations, and psychological problems such as mood changes, irritability, sleep disturbance, depression and decreased libido. Many women suffer from vaginal dryness and dyspareunia, which serve to enhance the loss of libido, and this in turn can adversely affect psychological well-being. The urethral mucosa may become atrophied, leading to an increased incidence of urinary tract infections or urinary incontinence. In some women, the urethra may eventually become fibrosed, leading to dysuria, frequency and urgency (urethral syndrome). The long-term consequences of oestrogen deprivation are often symptomless. There is a significant loss of calcium from the bones, which may give rise to frequent fractures, and there is a change in the blood lipid profile, which is associated with a rise in coronary heart disease.

Physiological changes

Ovarian

The approaching menopause is associated with loss of ovarian follicular activity. Human ovaries contain approximately 700,000 follicles at birth, but these cells have a high mortality rate and fewer than 500 of them will be ovulated. This number falls progressively with increasing age so that by the time the woman approaches 50 years of age, the number of follicles has fallen to zero or very few. The rate of follicle loss is highest during the decade between 40 and 50 years of age, possibly

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due to an increase in the rate of degeneration (atresia) of the earliest follicles. Women over the age of 45 years who are menstruating regularly have been shown to have 10 times as many follicles as those with irregular cycles; those who have not had a period for 12 months have few follicles remaining. Thus, the size of the follicular pool is an important determinant in ovarian function.

Ovarian function includes two major roles: the production of eggs (gametogenesis) and the synthesis and secretion of hormones (hormonogenesis). Both of these functions undergo subtle changes with ageing so that fewer ova are produced and they are less readily fertilised, and the hormone levels become irregular. It is the granulosa cells in the developing follicle that normally secrete estradiol, and lack of this follicular activity results in diminishing oestrogen secretion. The diminution in the number of active follicles is followed by an increase in follicle-stimulating hormone (FSH) secretion from the anterior pituitary gland as the normal feedback mechanisms between ovarian estradiol secretion and the hypothalamus–pituitary axis become disrupted. It may be that there is an age-related decrease in sensitivity to feedback inhibition that exacerbates this increase in FSH levels. In women who are still bleeding, an FSH level exceeding 10–12 iu/L on day 2 or 3 of the bleed is indicative of a diminished ovarian response. A high FSH level (above 30 iu/L) and a low estradiol level (below 100 pmol/L) in the plasma characterise menopause. The low oestrogen level fails to stimulate growth of the uterine endometrium. As endometrial growth has not occurred, there can be no menstruation (shedding of the endometrium) and this signifies that menopause has arrived. Since ova are not being released, the production of progesterone from the ovary also ceases and the levels of luteinising hormone (LH) eventually rise. Thus, peri-menopausal and menopausal women are subjected to an increasing ovarian hormone deficiency, as shown in Table 46.1.

When the ovaries are conserved after hysterectomy they will usually continue to produce some estradiol, but the levels of this hormone will decline up to the age of the natural menopause. Post-menopausally, in all women, androstenedione (secreted from the adrenal cortex) is converted in adipose tissue and muscle (peripheral conversion) to estrone, which becomes the major circulating oestrogen (but estrone is about 10 times less potent than estradiol). The levels of FSH and LH remain elevated for many years if no HRT is given, but these elevated levels have no effect on the ovary since the follicles are atretic.

Table 46.1 Ovarian hormone secretion after the onset of the normal menstrual cycle

	Pre-menopausal (normal cyclic)	Peri-menopausal (irregular cycles)	Post-menopausal (cessation of cycle)
Oestrogens	+++	++	+→–
Progesterone	+++	+	–
Androgens	+	+	+→–

The cessation of reproductive function in the woman and the declining oestrogen production from the ovary are not the only physiological events associated with menopause. For many years, oestrogen was considered to be associated only with the genitourinary system, but its effects are more wide ranging and the major tissues affected include blood vessels, bones and the brain.

Urogenital system

With the failure in ovarian oestrogen production, the number of uterine endometrial oestrogen receptors occupied falls and endometrial growth is not sustained. Thus, in the post-menopausal woman, the endometrium becomes thin and atrophic. Likewise, in the other target tissues containing oestrogen receptors, the basal layers of the vaginal epithelium are no longer stimulated to maintain the vaginal epithelium and produce natural lubricants from the vaginal glands. The result is vaginal atrophy and a thin, dry vagina may result in dyspareunia. Because the lower urinary tract and the lower genital tract share common embryological origin, deprivation of oestrogen can result in urethral and bladder problems. Often, peri-menopausal and post-menopausal women report an increase in urinary frequency, nocturia and urge incontinence. For some women, these changes may become manifest as long as 10 years after menopause.

Bone

Osteoporosis is defined by WHO as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. In 2006, WHO estimated that it affects 200 million women worldwide. In addition, approximately 30% of women over the age of 50 have one or more vertebral fractures compared with one in five men over the age of 50 who will have an osteoporosis-related fracture in their remaining lifetime. The total number of hip fractures in 1950 was 1.66 million, and by 2050, this figure could reach 6.26 million. Twenty percent of people die within 1 year of a hip fracture (Cooper, 1997). Typical morbidities after a vertebral fracture include:

- back pain
- loss of height
- deformity (kyphosis, protuberant abdomen)
- reduced pulmonary function
- diminished quality of life: loss of self-esteem, distorted body image, dependence on narcotic analgesics, sleep disorder, depression, loss of independence.

To contextualise risk, the remaining lifetime probability in women at menopause of a fracture at any one of these sites exceeds that of breast cancer (~12%). Also, the likelihood of a fracture at any of these sites is 40% or more in developed countries (Kanis et al., 2000), a figure close to the probability of

coronary heart disease. Risk factors for osteoporosis include low body mass index (<19 kg/m^2), smoking, early menopause, family history of maternal hip fracture, long-term systemic corticosteroid use and conditions affecting bone metabolism, especially those causing prolonged immobility. Osteoporosis is most common in white women. People with osteoporosis are at risk of fragility fractures, occurring as a result of mechanical forces which would not ordinarily cause fracture. The clinically relevant outcome in evaluating treatments for osteoporosis is the incidence of fragility fracture as otherwise this condition is asymptomatic and therefore undiagnosed. The most common sites for these fractures are the hip, vertebrae and wrist. In the UK, the combined cost of hospital and social care for patients with a hip fracture amounts to more than £1.73 billion per year (Torgerson et al., 2001). This is very similar to the annual £1.75 billion health care system costs of coronary heart disease costs. The cost of treating all osteoporotic fractures in post-menopausal women has been predicted to increase to more than £2.1 billion by 2020 (Burge, 2001).

Cardiovascular system

Young adult women are protected against the development of hypertension and its deleterious consequences in the cardiovascular system. Levels of low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) are decreased by oestrogen, and the levels of high-density lipoprotein cholesterol (HDL-C) are increased, thereby giving some protection against atherosclerosis. HDL-C is known to promote cholesterol efflux from macrophages in the arterial wall, thereby reducing atheromatous plaque and conferring a protective effect against heart disease. However, after menopause, this protection is lost and the incidence of high blood pressure and associated cardiovascular disease increases to levels similar to those found in age-matched men.

Oestrogen has direct beneficial effects in the control of blood pressure, possibly via regulating endothelium-mediated control of arteriolar tone. In women deprived of oestrogen, endothelium-dependent vasodilation is impaired. This dysfunction is largely associated with a reduction in nitric oxide availability. Oestrogen increases nitric oxide availability by stimulating endothelial nitric oxide synthase (eNOS). Oestrogen also stimulates the production of other endothelium-derived relaxing factors such as prostacyclin (prostaglandin I_2). Research suggests that the oestrogen receptor (ER)α is important in mediating the vascular effects of oestrogen. Studies using selective ERα agonists are being undertaken. However, many pathways are stimulated by oestrogen receptor activation and the relative importance of these different pathways varies from tissue to tissue.

Miscellaneous

Thinning of the skin, brittle nails, hair loss and generalised aches and pains are also associated with reduced oestrogen levels (Hall and Phillips, 2005). The skin is the largest non-reproductive target on which oestrogen acts. Oestrogen receptors, predominantly of the ERβ type, are widely distributed within the skin. Both types of oestrogen receptor (ERα and ERβ) are expressed within the hair follicle and associated structures. Thus, epidermal thinning, declining terminal collagen content, diminished skin moisture, decreased laxity and impaired wound healing (selective ERα ligands are being investigated for their wound-healing properties) have been reported in post-menopausal women.

In addition, women also show increasing body weight associated with ageing. This weight gain tends to increase or begin near menopause. Body fat redistribution to the abdomen also occurs independent of weight gain. This type of centralised abdominal fat distribution is widely recognised as an independent risk factor for cardiovascular disease in women.

Psychological changes

Older age at menarche and younger age at menopause are associated with poorer cognitive functioning during ageing. Recent studies have demonstrated that sex steroids have a multifarious and complex relationship with the central nervous system (Hogervorst et al., 2009). For example, there may be a positive correlation between increasing parity and improved executive functioning in response to oestrogen. This temporal relationship between oestrogen deprivation and response to exogenous oestrogen was clearly exemplified in the memory study arm of the WHI (Coker et al., 2010) and MWS studies (Hogervorst and Bandelow, 2010) at the turn of the twenty-first century.

Depression is twice as common in women as in men and may increase during times of changing hormonal levels such as at menopause. Some aspects of decreased central nervous system function have been related to falling oestrogen levels. Preclinical studies have shown oestrogen to have several positive effects on central nervous system function. Perhaps the most important is promotion of acetylcholine synthesis and increased synaptogenesis in the hippocampus. ERβ is expressed in this area of the brain as well as the entorhinal cortex and thalamus, areas crucially involved in explicit memory. Human neuroimaging studies have also indicated that oestrogen influences regional cerebral blood flow in women.

Management

Hormone replacement therapy

HRT is a complicated clinical issue requiring an in-depth risk/benefit assessment. The vast amount of study data are often conflicting, and careful analysis is required. Many factors need to be reviewed before it is prescribed. One important factor is age, as data have shown that if a woman aged less than 35 has a hysterectomy and a bilateral oophorectomy, her risk of non-fatal myocardial infarction is nearly eight times that of her age-matched counterpart who has retained her ovaries. Age at time of HRT prescription in relation to menopausal age, that is, number of years of oestrogen deprivation before

replacement, is also of importance when considering outcomes. Individual differences in hormone metabolism (both endogenous and exogenous) are also likely to be important as several different cytochrome enzymes metabolise oestrogen and may be affected by inherited polymorphisms. Therefore, some women may produce oestrogenic metabolites possessing considerable oestrogenic activity, whilst others produce metabolites which are relatively non-oestrogenic. Body mass index (BMI) also influences response to HRT, with increased plasma estradiol levels observed in women with higher BMIs.

HRT is effective for symptomatic relief of menopausal symptoms, and its use is justified when symptoms adversely affect quality of life. Current advice is that the lowest effective dose for a particular woman should be used for the shortest period of time. Local oestrogen replacement may be used to reverse the symptoms of urogenital atrophy as it appears to be more effective than systemic therapy. There is no evidence to suggest that local oestrogen treatment is associated with significant risks.

Treatment with HRT should be reviewed at least annually, with alternative therapies considered for the management of osteoporosis. In the treatment of menopausal symptoms, the benefits of short-term HRT outweigh the risks in the majority of women, but in healthy women without symptoms, the risks outweigh the benefits.

Contraindications to the use of HRT include undiagnosed vaginal bleeding in post-menopausal women, the presence of an oestrogen-dependent tumour, liver disease (where liver function tests have failed to return to normal), active thrombophlebitis, and active or recent arterial thromboembolic disease, for example, angina or myocardial infarction. A history of deep vein thrombosis and pulmonary embolism requires careful evaluation before the use of oestrogen therapy. Use in patients with Dubin–Johnson and Rotor syndromes may also be contraindicated.

Oestrogen therapy

Since the symptoms and long-term effects of menopause are due to oestrogen deprivation, the mainstay of HRT is oestrogen. This may be administered orally or parenterally but, in either case, the oestrogens used are naturally occurring and include:

- estradiol
- estriol
- estrone
- estropipate
- conjugated equine oestrogen (estrone sulphate 40%, equilin sulphate 60%)
- estradiol valerate.

The use of 'natural' oestrogens reduces the risk of the potentially dangerous oestrogenic effects such as raised blood pressure, alteration in coagulation factors and an undesirable lipid profile, which sometimes occur with the more potent synthetic oestrogens used in the oral contraceptive agents. A 'natural' oestrogen is defined as one that is normally found in the human female and has a physiological effect. Natural oestrogens are less potent (up to 200 times) than synthetic oestrogens. As they are naturally occurring compounds, the plasma half-life of these oestrogens is similar to that of the ovarian-secreted oestrogens and the duration of action is shorter than the synthetic oestrogens, such as ethinylestradiol, used in many formulations of the contraceptive pill. The plasma ratio of estradiol to estrone is normally about 1:1 to 2:1, and the aim of HRT should be to preserve this ratio.

There are four main routes of administration for oestrogens in HRT:

- oral
- transdermal (patches/gels/cream)
- subcutaneous (implants)
- vaginal (creams and medicated rings).

The use of oral oestrogen therapy, while convenient for the patient, does mean that the oestrogen will be subjected to conversion to estrone by the liver and the gut, thereby altering the estradiol:estrone ratio in favour of the less active oestrogen, estrone. The oral preparations have different metabolic effects due to first-pass hepatic metabolism. Smoking stimulates metabolism of oestrogens by cytochrome P450 and decreases plasma oestrogen levels by 40–70% in oral oestrogen users. Smoking has no significant effect on plasma oestrogen levels in users of transdermal preparations. Oral delivery compared to transdermal delivery (Table 46.2) also has different effects on lipid levels (Vrablik et al., 2008). In addition, orally administered oestrogens undergo first-pass hepatic metabolism, which may result in some reduction in anti-thrombin III, a potent inhibitor of coagulation. Implants and patches show smaller changes in coagulation, platelet function or fibrinolysis.

More constant levels of oestrogen result from the use of transdermal patches containing estradiol, and these have the added advantage of a more physiological estradiol:estrone ratio (Delmas et al., 1999). However, the adhesive used in these transdermal patches and the alcohol base can cause skin irritation. The patch is applied to the non-hairy skin of the lower body, and care should be taken to ensure that it is placed away from breast tissue. The patch is changed either once or twice a week, thus providing a constant reservoir of estradiol to provide a controlled release into the circulation. Estradiol is also available in a gel formulation, applied daily to the skin over the area of a template (to ensure correct dosage), but

Table 46.2 Effect of HRT administration route on lipid profile

Oral	Transdermal
↓ Low-density lipoprotein	↓ Low-density lipoprotein
↓ Total cholesterol	↓ Total cholesterol
↑ High-density lipoprotein	↔ High-density lipoprotein
↑ Triglycerides	↓ Triglycerides
↑ Bile cholesterol	↔ Bile cholesterol

this formulation may give erratic absorption. The intranasal preparation, administered as a nasal spray, also avoids hepatic first-pass metabolism.

The oestrogen implant gives a constant level of oestrogen from a few days after insertion for up to 6 months. This formulation maintains the best estradiol:estrone ratio and is a convenient method of administration, requiring repeat implants only every 6 months. However, because the levels of oestrogen are constantly raised, there will be some increase in oestrogen receptor numbers, and this can lead to a recurrence of symptoms of oestrogen deficiency due to the presence of unoccupied oestrogen receptors, even in the presence of normal or even high oestrogen levels. This phenomenon, called tachyphylaxis, results in patients becoming symptomatic and requesting repeat implants earlier and earlier. In such cases, it is unwise to treat with additional oestrogen; the patient should receive counselling and perhaps a change of preparation. The disadvantage of the implant is that, once inserted, it cannot be removed readily and even if it is removed, the oestrogen level will take at least a month to fall. There is also evidence that the uterine endometrium, if present, remains stimulated for some time after removal of the implant.

Both the transdermal and implant preparations avoid the first-pass hepatic effects of oral oestrogens and are less likely to affect liver enzyme systems and clotting factors. Some studies show an increase in the incidence of venous thromboembolism (VTE) in women taking HRT. Therefore, patients who have a history of deep vein thrombosis or pulmonary embolism will need careful guidance, with each woman being considered individually, and the relative risks evaluated. Other risk factors include severe varicose veins, obesity or a family history of deep vein thrombosis (DVT). If HRT is justified in such patients, transdermal preparations are a better alternative than oral preparations.

Vaginal creams containing oestrogen are available but generally fail to produce the reliable plasma levels required to protect against the long-term effects of oestrogen deprivation. They provide short-term relief from menopausal symptoms, in particular, atrophic vaginitis. A vaginal ring which releases estradiol at a controlled rate in physiological levels for up to 3 months is an alternative for women who cannot tolerate transdermal patches.

The dose of oestrogen used in HRT sufficient to preserve bone density is usually higher than that necessary to alleviate vasomotor symptoms. The doses suggested to protect bone density are estradiol 2 mg/day orally, 50 μg/day transdermally and 50 mg every 6 months by implant. If the conjugated equine oestrogens are used, the oral dose should be 0.625 mg/day. The lower doses found in vaginal creams may alleviate the vasomotor symptoms but will not protect against osteoporosis. Current guidelines advise the use of the lowest possible dose of HRT to relieve vasomotor symptoms and recommend alternative treatment to prevent and treat osteoporosis.

Oestrogens should be used alone only in women who have undergone a hysterectomy; if the uterus is present, the endometrium will be stimulated and this increase in endometrial growth may be a precursor to development of a malignant condition. Current practice is to administer progestogens with oestrogen. In the early 1970s, when oestrogen was used alone, HRT received a bad press because in women who had not undergone hysterectomy, there was an increased incidence of endometrial carcinoma. In women who have undergone hysterectomy, oestrogens are usually administered continuously.

Progestogen therapy

The only proven reason for adding a progestogen to oestrogen therapy for HRT in women with an intact uterus is to protect the endometrium from hyperplasia and possible neoplasia. There are many preparations which contain progestogens added to oestrogen for a number of days per month. However, to effectively prevent endometrial hyperplasia, the progestogen must be taken for a minimum of 12 days. The minimum dose of progestogen required to protect against hyperplasia depends on the potency of the compound used.

The progestogens commonly available in HRT preparations are either derivatives of progesterone, such as medroxyprogesterone and dydrogesterone, or 19-nortestosterone substitutes such as norethisterone or levonorgestrel. All these synthetic progestogens are active following oral administration and provide adequate protection of the endometrium against oestrogen stimulation. Some transdermal preparations also incorporate a progestogenic compound in the regimen. As with all semi-synthetic or synthetic hormones, these compounds may act on receptors other than the progesterone receptor, and the long-term consequence of this is not predictable.

Progesterone is the only progestogen to act solely on the progesterone receptor, but it has poor oral bioavailability and so it is difficult to achieve satisfactory plasma concentrations. However, the micronised preparations are better absorbed. Progesterone may also be administered at night in the form of a pessary or suppository, or by injection in the form of a long-lasting subdermal implant. The progestogen in HRT is most commonly administered orally or transdermally and usually one of the synthetic progestogens is used.

Oestrogen and progestogen regimens

The monthly withdrawal bleed is perceived by some postmenopausal patients to be an unacceptable side effect of HRT, and this has resulted in the development of a number of regimens in an effort to minimise this effect (Box 46.1). Formulations have been produced with which bleeding only occurs every 3 months instead of every 4 weeks, or it does not occur at all.

Box 46.1 Regimens of combined oestrogen and progestogen therapy for use in HRT

- Oestrogen 28 days + progestogen 12 or 14 days, then repeat without interval (bleed every 4 weeks)
- Oestrogen 70 days + progestogen 14 days followed by 7 days placebo tablets (bleed every 3 months)
- Oestrogen + progesterone continuously (no bleed)
- Oestrogen continuously + Mirena IUS (bleed variable but levonorgestrel likely to reduce bleed and can provoke amenorrhoea)

The use of the 70-day oestrogen preparation, while being more popular with women because bleeding only occurs every 3 months, needs further evaluation as regards endometrial protection. Bleeding can be avoided altogether if a combination of oestrogen and progestogen is given continuously throughout the treatment (continuous combined HRT). Such a preparation should only be given to women who are at least 12 months post-menopausal and have an atrophied endometrium; otherwise, breakthrough bleeding may occur. Bleeding in the first 6 months (usually just spotting) is not uncommon but bleeding after this time should be investigated, although the incidence of endometrial hyperplasia is low with this continuous regimen. Others recommend a 28-day interval between courses of treatment to allow the endometrium to become atrophic in patients who are changing from the cyclical therapy to the continuous combined therapy. Patients who commence cyclical HRT prior to ceasing menstruation should change to a continuous combined preparation only after the age of 54 (when there is an 80% chance that they will be post- rather than peri-menopausal) to reduce the risk of breakthrough bleeding. An alternative option is to use the levonorgestrol-loaded intrauterine system (IUS or Mirena) in conjunction with oral oestrogen. This option can be particularly useful for women intolerant of progestogenic side effects.

Not all progestogens have the same pharmacological profile and these differences have implications for their usage. Two of the most widely used synthetic progestogens are medroxyprogesterone acetate and norethisterone. These are used as the progestogenic component of an HRT regimen in combination with oestrogen but have been shown to increase the risk of breast cancer in long-term HRT users (Million Women Study Collaborators, 2003; Women's Health Initiative, 2002). Structurally, medroxyprogesterone acetate is more similar to natural progesterone than norethisterone. The metabolism of these two compounds is also different, as medroxyprogesterone acetate is the major progestogenic compound rather than one of its metabolites. In contrast, the metabolites of norethisterone exhibit significant activity in addition to a wide range of non-progestogenic actions. Norethisterone also binds to sex hormone–binding globulin, whereas medroxyprogesterone acetate does not.

The most notable difference in steroid receptor-binding affinity between the two synthetic progestogens and endogenous progesterone is that although all the compounds have affinity for the mineralocorticoid receptor, only the natural compound has antagonist activity. As a consequence, the synthetic compounds may be unable to counteract the sodium-retaining and blood pressure–raising effects of the oestrogens used in HRT. Endogenous progesterone affinity for the glucocorticoid receptor is also different, with medroxyprogesterone acetate a more potent antagonist than norethisterone. This may influence their side-effect profiles and impact on inflammation, immune response, adrenal function and bone metabolism.

Tibolone

Tibolone is a synthetic steroid that has oestrogenic, progestogenic and androgenic effects that alleviate menopausal symptoms without a monthly bleed. The oestrogenic effects are weak and should not promote endometrial hyperplasia, but 10–15% of women on this treatment experience breakthrough bleeding. The drug is given continuously but is not suitable for women within 1 year of menopause or immediately after oestrogen therapy because in such cases breakthrough bleeding is most likely to occur. The evidence suggests that this drug is protective against osteoporosis, but the long-term cardioprotective effects remain unclear as there is some evidence of a lowering of HDL-C. It should also be withdrawn if signs of thromboembolic disease occur. The androgenic action of tibolone tends to increase libido. It has been reported that tibolone does have fewer breast-related adverse effects than oestrogenic or oestrogenic–progestogenic HRT regimens.

Raloxifene

Raloxifene is a non-steroidal benzothiophene that binds to some oestrogen receptors and belongs to a class of drugs referred to as selective oestrogen receptor modulators (SERMs). These compounds act selectively on some oestrogen receptors to increase bone mineral density and antagonise oestrogen-dependent effects on breast and endometrial tissues in post-menopausal women. However, there is a reported increased risk of thromboembolism, particularly in the first 4 months of use. Raloxifene cannot be used to treat vasomotor symptoms in peri-menopausal women. In fact, it is reported to induce hot flushes. It has little or no stimulatory effect on the uterine endometrium and is not associated with uterine bleeding.

In summary, raloxifene is a compound that selectively stimulates one group of oestrogen receptors and may be considered a curative treatment for osteoporosis and a preventive agent in the development of oestrogen-dependent breast tumours.

Clinical monitoring

Before initiating HRT, a detailed patient history and physical examination are essential to eliminate medical disorders and genital malignancy. Bone mineral densitometry can also be helpful to establish a baseline for subsequent measurements. Blood tests should include serum electrolytes and creatinine, liver function tests, haemoglobin, lipids and a full blood count. Urine analysis should also be performed. The history and findings from the physical examination may indicate other tests. The patient should have undergone routine cervical smear examination and, preferably, mammography. In women with an intact uterus, any irregular vaginal bleeding should be investigated to exclude endometrial pathology.

After starting therapy, the woman should be seen within 3 months in the first instance and then at intervals between 6 and 12 months so that symptoms may be assessed and any side effects of therapy can be reported. Blood pressure

measurements are undertaken on these routine visits; HRT is usually associated with a fall in blood pressure due to a vasodilator action of oestrogen. Hypertension is not a contraindication to treatment with HRT but does need treatment before starting on oestrogen therapy. Some women may have an elevated blood pressure on oral oestrogen but show no such effect with the non-oral route. Weight gain may occur some months after treatment has been initiated, and the patient should be advised to reduce calorie intake accordingly.

Stopping HRT

Guidelines (see Section 7.3.1 British National Formulary) indicate that there are a number of signs and symptoms which suggest that women should be advised to immediately stop taking HRT and these include:

- sudden severe chest pain
- sudden breathlessness or cough with blood-stained sputum
- unexplained severe pain in calf of one leg
- severe stomach pain
- serious neurological effects
- hepatitis, jaundice, liver enlargement
- blood pressure above systolic 160 mmHg and diastolic 100 mmHg
- detection of a risk factor, for example, prolonged immobility after surgery or leg injury.

Once HRT has been stopped, investigation and treatment should be undertaken as appropriate.

Examples of serious neurological effects include unusual severe, prolonged headache. This is especially important if the headache occurs for the first time or it becomes progressively worse. Marked numbness, especially if it suddenly affects one side or part of the body, is important. Other neurological effects are sudden partial or complete loss of vision or disturbance of hearing or other perceptual disorders. HRT should also be stopped if the following occur: dysphasia, bad fainting attack or collapse, a first unexplained epileptic seizure/weakness and motor disturbances.

Alternatives to HRT

HRT remains the most effective treatment for vasomotor symptoms, resulting in 80–90% reduction in hot flushes. Of the non-hormonal agents, serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and its active metabolite desvenlafaxine appear to be the next most useful treatments; gabapentin may be equally effective, whilst clonidine is only modestly effective in reducing hot flushes. Generally, there is a lack of safety information and trial data regarding alternative therapies. Trials with black cohosh, red clover and soy foods, all of which contain phytoestrogens, have yielded conflicting results and have raised concerns about hepatoxicity (black cohosh) and interactions with anti-coagulants (red clover).

Bisphosphonates such as alendronate, etidronate and risedronate are inhibitors of bone resorption and increase bone mineral density by altering osteoclast activation and function. Bisphosphonates are used with care in women with upper gastro-intestinal problems and their posology is complex. They are contraindicated in patients with hypocalcaemia. Etidronate is also contraindicated in patients with severe renal impairment.

Teriparatide, a recombinant human parathyroid hormone, is licensed to treat osteoporosis in post-menopausal women. It stimulates new formation of bone and may increase resistance to fracture. However, it has several contraindications including hypercalcaemia, severe renal impairment, metabolic bone diseases and unexplained elevations of alkaline phosphatase.

A Cochrane review supports the efficacy of strontium ranelate for the reduction of fractures in post-menopausal osteoporotic women (O'Donnell et al., 2006). The main side effect reported was diarrhoea, but the potential vascular and neurological side effects should be explored further. National guidance (NICE, 2010) details the role of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in post-menopausal women.

Advances in bone biology may lead to the design of more elegant therapies to deal with osteoporosis. An example would be denosumab, a human monoclonal antibody which binds to the receptor activator of nuclear factor-κβ ligand (RANKL), which is responsible for osteoclast differentiation, activation and survival. Denosumab therefore mimics the function of osteoprotegerin limiting bone resorption.

Some small studies have shown that aerobic exercise can improve cardiovascular parameters and reduce menopausal symptoms in addition to reducing BMI.

Treatment with HRT

Vasomotor symptoms

Vasomotor symptoms include hot flushes, headaches, insomnia, giddiness and faintness. They occur in about 70–80% of women and result in physical distress in about 50%, lasting for up to 5 years in around one-quarter of the women. Flushes and sweats, particularly night sweats, indicate vasomotor instability and probably result from unoccupied oestrogen receptors on blood vessels. Oestrogens cause a rapid rise in blood flow through the blood vessels, and lack of oestrogen will render the oestrogen receptors in these vessels supersensitive to any subsequent rise in oestrogen level. During the perimenopause and menopause, oestrogen levels tend to fluctuate and it is suggested that it is these fluctuations that result in vasomotor symptoms. The extreme sensitivity of blood vessel oestrogen receptors tends to mean that a clinical response to vasomotor symptoms is achieved with low doses of oestrogen. There is also likely to be central control via a supra-pituitary mechanism incorporating several chemical pathways involving serotonin, noradrenaline and dopamine. General advice

regarding diet, for example, avoiding certain foods and drinks that cause vasodilation such as hot spicy foods and alcohol, may be helpful to some women. There is some evidence that regular exercise, which stimulates the production of hypothalamic β-endorphins, may reduce the risk of hot flushes.

Urogenital tract

These symptoms include:

- vaginal dryness and dyspareunia (painful sexual intercourse)
- vaginal discharge and bleeding
- urinary incontinence, urgency of micturition, recurrent symptoms of cystitis.

Symptoms result from oestrogen deficiency in menopausal woman and may be treated either with systemic HRT preparations or with topical applications of oestrogen incorporated into vaginal creams, pessaries and silicone vaginal rings. Such topical routes of administration do result in some systemic absorption of oestrogen through the vaginal mucosa and since this may be erratic, vasomotor symptoms may ensue. Absorption of oestrogen from these topical applications may also stimulate uterine endometrial development, if present. Consequently, it is recommended that these treatments should not be used for more than 6 months. The dose of oestrogen required to stimulate the oestrogen receptors in the vagina and the lower urethra is about 10 μcg/day, and the efficiency of such low doses has been demonstrated in a number of clinical trials. The effect of oestrogen on vaginal symptoms is more marked than its effect on urinary symptoms, but the incidence of urinary sensory dysfunction may be improved. Menopausal atrophic vaginitis may respond to a short course of a topical vaginal oestrogen preparation used for a few weeks and repeated if necessary. Current guidance is that the minimum effective dose should be used for the shortest duration.

Initial treatment with local oestrogen may result in a reaction to the presence of oestrogen in tissues containing oestrogen receptors, such as the breast and vagina. The longer the time between starting HRT and menopause, the greater these effects. During initial treatment, other effects observed include headache, appetite increase and calf muscle cramps, but these side effects usually resolve without intervention. HRT with small doses of an oestrogen (together with a progestogen in women with an intact uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability.

Bone

In a woman not treated with HRT, approximately 15% of bone mass is lost within 10 years of menopause, resulting in an increased incidence of fracture, typically of the hip. Such fractures take up at least 10% of orthopaedic beds, and the total cost in terms of morbidity and mortality is high. The effect of oestrogen lack is to increase osteoclastic bone resorption. There is an overall increase in bone turnover, more bone is resorbed than replaced and there is an associated increase in the rate of bone loss which may continue for 5–10 years. Oestrogens may exert effects on bone through the calcium-regulating hormones such as calcitonin and parathyroid-regulating hormones. Evidence also exists for the effect of oestrogens on the local production of bone growth factors, cytokines, in particular osteoprotegerin, which blocks osteoclastogenesis and prostaglandin E_2.

The greatest effect of oestrogen on bone is seen with implants, where an approximately 8% increase in vertebral bone density is seen within 1 year of treatment. Estradiol patches are the next most effective route of administration (Fig. 46.1), while oral therapy only achieves an increase in bone density of about 2% per annum. However, 5 years of oral oestrogen therapy will still achieve a lifetime reduction in femoral neck fracture of as much as 50%.

Oestrogen improves the quality and quantity of bone in the post-menopausal woman. It may be started at any time after menopause, and the benefit will continue for the duration of treatment. Bone loss will continue after treatment ceases, which leads into the difficult area of how long treatment should continue. It was previously recommended that to obtain maximum benefit from treatment with oestrogen, the duration of the course should be at least 10 years. However, studies have identified some potential adverse effects of HRT (Million Women Study Collaborators, 2003; Women's Health Initiative, 2002). Therefore, this recommendation is controversial, particularly in women with an intact uterus, where a combined HRT preparation is required as there is probably a greater risk of adverse outcome. Oestrogen given systemically in the peri-menopausal and post-menopausal period or tibolone given in the post-menopausal period also diminishes post-menopausal osteoporosis, but other drugs are preferred.

Raloxifene is licensed for the prevention and treatment of osteoporosis as an alternative to HRT. Raloxifene reduces bone loss and increases bone density at the spine and hip in post-menopausal women. With its oestrogen antagonist effect on breast and endometrium, raloxifene may prove to be an advance over oestrogen treatment in osteoporosis prevention and treatment in post-menopausal women. It does, however, cause hot flushes which may be unacceptable for some.

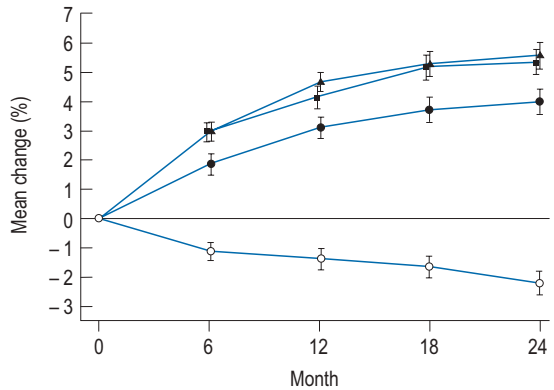


Fig. 46.1 Percentage of change from baseline (mean ± SEM) in lumbar spine bone mineral density in patients receiving placebo (open circles) or transdermal 17β-estradio 50 μcg/day (filled circles), 75 μcg/day (squares) or 100 μcg/day (filled triangles) (from Delmas et al., 1999).

Cardiovascular system

The estimated influence of HRT on the incidence of coronary heart disease, venous thromboembolism and stroke is summarised in Table 46.3.

Coronary heart disease

Women at 45 years are significantly less likely than men to die of coronary heart disease, but by the age of 60 years, the death rate from the disease is similar in both sexes. Oestrogen is probably central to this gender difference as women who experience early loss of endogenous estradiol have an accelerated risk of developing coronary heart disease. Intuitively, it would appear logical that post-menopausal women would gain benefit from receiving exogenous oestrogen. However, there are conflicting views as to whether this is, or is not, the case. A 4-year study of women with coronary heart disease in the USA (Heart and Estrogen-Progestin Replacement Study, HERS) who were also receiving HRT (conjugated equine oestrogen and medroxyprogesterone acetate) demonstrated no significant reduction in stroke (Simon et al., 2001). This was in contrast to the increased risk of myocardial infarction in the first year of starting HRT in the original HERS report (Hulley et al., 1998). The Women's Health Initiative (2002), another US-based study, also reported an increase in coronary events in the first year of receiving HRT.

The relevance of both studies to UK practice has been challenged as both involved use of conjugated equine oestrogen/medroxyprogesterone acetate regimens. In the UK, natural progesterone is preferred, and this differs from medroxyprogesterone acetate in that it does not attenuate the beneficial effects of oestrogen in reducing the development of coronary artery atherosclerosis and protecting against coronary vasospasm. A study (De Vries et al., 2006) using the UK General Practice Research Database found HRT was associated with a decrease in risk of acute myocardial infarction, and there was no difference between the different oestrogen–progestogen combinations. A recent study found that transdermal but not oral oestrogen replacement therapy significantly reduced atherogenic index of plasma (Vrablik et al., 2008). This occurred by increasing HDL particle size and therefore improving the antiatherogenic properties.

The International Menopause Society consensus statement (2009) states that HRT can be given to women around the age of natural menopause without increasing the risk of coronary heart disease and may even decrease the risk in this age group. HRT is not contraindicated in women with hypertension, and in some cases, HRT may even reduce blood pressure. HRT is contraindicated in women with a history of myocardial infarction, stroke or pulmonary embolism.

Venous thromboembolism

It is known that the oestrogen in the combined oral contraceptive pill contributes to thromboembolic disorders. Whether the same applies to the oestrogen in HRT is unclear as the dose of oestrogen found in HRT is much lower and more physiological than that in the oral contraceptive pill. Analysis of the results from the Women's Health Initiative (2002) has confirmed that there is an increased risk of pulmonary embolism with HRT and the risk is greater with oral HRT than transdermal oestrogen.

Table 46.3 Estimated influence of HRT on incidence of gynaecological cancers, venous thromboembolism, stroke and CHD (MHRA/CHM, 2007)

Risk	Age range (years)	Background incidence per 1000 women in Europe not using HRT		Additional cases per 1000 women using oestrogen only HRT (estimated)		Additional cases per 1000 women using combined (oestrogen-progestogen) HRT (estimated)	
		Over 5 years	Over 10 years	For 5 years' use	For 10 years' use	For 5 years' use	For 10 years' use
Breast cancer	50–59	10	20	2	6	6	24
	60–69	15	30	3	9	9	36
Endometrial cancer	50–59	2	4	4	32	NS	NS
	60–69	3	6	6	48	NS	NS
Ovarian cancer	50–59	2	4	<1	1	<1	1
	60–69	3	6	<1	2	<1	2
Venous thromboembolism	50–59	5		2		7	
	60–69	8		2		10	
	60–69	9		3		3	
Coronary heart disease	70–79	29–44		NS		15	

Note: Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference.

Oral oestrogen, in contrast to the transdermal route, undergoes extensive first-pass metabolism. This increases the production of prothrombotic factors in the liver and is associated with a reduction in fibrinogen and factor VII activation, such as von Willebrand's factor and anti-thrombin, and enhanced fibrinolysis (RCOG, 2004). HRT is also associated with increased resistance to activated protein C.

Whilst oestrogen exposure and age increase the risk of venous thromboembolism, they do not explain the increased risk seen in the first year of HRT use. An underlying thrombophilia, a known risk in hyperoestrogenic situations, is thought to be the additional factor that makes certain women susceptible to venous thromboembolism. Guidelines (RCOG, 2004) to manage the risk of venous thromboembolism have been produced for women starting or continuing HRT (Box 46.2). The selective oestrogen receptor modulators (SERMS) such as raloxifene are considered to carry the same risk of thrombosis as oestrogen-containing HRT.

Overall, minimising cardiovascular risk whilst obtaining the benefits of HRT is influenced by the age of the women treated, their body mass index, cardiovascular health and menopausal history, the timing of initiation of HRT, the formulation of the product used, and polymorphism.

Table 46.4 Properties of progestogens and their link to breast cancer (adapted from Campagnoli et al., 2005)

Progestogen	Action
19-Nortestosterone derivatives, medroxyprogesterone acetate	Oestrogenic activity Influence on 17β-hydroxysteroid dehydrogenase
19-Nortestosterone derivatives, medroxyprogesterone acetate	Metabolic effects, opposing those of oestrogen, on insulin sensitivity. Hepatic effects, opposing those of oestrogen, that is increasing IGF-1 (insulin-like growth factor), decrease in sex hormone-binding globulin
19-Nortestosterone derivatives	Binding to sex hormone-binding globulin with consequent reduction in capacity to bind oestrogen

Cancer

Details of the estimated influence of HRT on the incidence of cancer are presented in Table 46.3.

Colorectal cancer

Colorectal cancers tend to occur in women over 50, and several studies have indicated that HRT can reduce the risk by around 35%. The exact mechanism for this protective effect on the colon is unclear, although it has been suggested that oestrogen may decrease the formation of potentially carcinogenic bile acids.

Ovarian cancer

The risk of ovarian cancer risk is known to be affected by exogenous hormones, with a reduced incidence consistently reported in users of oral contraceptives. The relationship between the hormones used in HRT and ovarian cancer is, however, less clear. Women who use oestrogen plus a progestogen do not appear to be at increased risk of ovarian cancer, perhaps because the progestogenic component has an apoptotic effect on the ovarian epithelium. This has been supported

Box 46.2 Summary of guidelines for dealing with the risk of venous thromboembolism (VTE) in women receiving HRT (adapted from RCOG, 2004)

Women starting or continuing HRT

- Women starting or continuing HRT should be counselled with regard to perceived benefits and possible risks for their individual situations, including consideration of alternative therapies.
- All women commencing HRT should be counselled about the risk of VTE, should be aware of the signs and symptoms of VTE and should be able to access medical help rapidly if they suspect that they have developed a thrombus.
- Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT is inappropriate.
- Prior to commencing HRT, a personal history and a family history assessing the presence of VTE in a first- or second-degree relative should be obtained.
- HRT should be avoided in women with multiple pre-existing risk factors for VTE.

Women with a personal or family history of VTE

- Testing for thrombophilia should be discussed with, and available for, women with a personal or family history of VTE.
- In women with a previous VTE, with or without underlying heritable thrombophilia, oral HRT should be usually avoided in view of the relatively high risk of recurrent VTE.
- In women with a personal history of VTE but with an underlying thrombophilic trait identified through screening, HRT is not recommended in high-risk situations such as anti-thrombin deficiency or with combinations of defects.
- In women over 50 years with a history of VTE within the previous year, a full clinical history and examination with appropriate investigations is warranted for underlying disease.
- If a woman who is on HRT develops VTE, HRT should be discontinued.
- If a woman wants to continue on HRT after VTE, long-term anti-coagulation should be considered.

by studies in small groups of women with a mutation in either the *BRCA1* or *BRCA2* gene (point mutations associated with breast and ovarian cancer) which demonstrated that HRT did not adversely influence the risk of developing ovarian cancer. In contrast, other large HRT trials have suggested a possible increase in risk of ovarian cancer, particularly in women who have had a hysterectomy and are receiving long-term oestrogen-only HRT.

Endometrial cancer

Unopposed oestrogen therapy at least doubles the risk of endometrial cancer, but the addition of a progestogen, either in continuous combined or sequential regimens, reduces this risk. Of the two regimens, continuous combined administration is more effective than sequential therapy in reducing the risk of endometrial hyperplasia.

Breast cancer

Breast cancer is the most common cause of disease and death in middle-aged women, affecting around one in 11 women before the age of 75 in developed countries. Over the past 20 years, there has been a growing body of evidence to suggest that progesterone contributes to the development of breast cancer. Evidence to support this came from trials in which use of combined regimens increased breast cancer risk more than oestrogen alone. This is thought to have occurred because the synthetic progestogens possessed some non-progesterone like effects that potentiated the proliferating action of oestrogen. In the USA, the most commonly used progestogen in HRT was medroxyprogesterone acetate combined with conjugated equine oestrogen and administered orally. In contrast, in central and southern Europe, a wider range of progestogens is used, particularly the 19-nortestosterone derivatives. Studies investigating the use of natural micronised progesterone to improve bioavailability in HRT regimens have demonstrated no increased risk of breast cancer. *In vitro* studies with medroxyprogesterone have found it promotes the reproductive transformation of estrone into estradiol by influencing the activity of 17β-hydroxysteroid dehydrogenase. The properties of the synthetic progestogens are outlined in Table 46.4.

The relationship between different HRT regimens and breast cancer is complex (Table 46.4). There are many potential confounders to be considered when interpreting trial data, for example, time of initiation of therapy, in relation to menopausal status, body mass index, prior hormone use, etc. Chlebowski et al. (2009) reported on the decline in breast cancer in the USA after a reduction in HRT usage following publication of the WHI trial (2002). This prompted a response from the President of the International Menopause Society (Sturdee, 2009) summarised as follows:

- Decline in breast cancer rates started at least 3 years before the WHI study was halted (which led to a dramatic drop in HRT use). This implies that decline in breast cancer rates must be independent of the reduction in HRT use.
- Breast cancer takes years to develop and at least a decade to reach the detectable stage. If HRT use causes breast cancer, then the drop in breast cancer rates would not be seen for some time.
- The drop in breast cancer rates could be due to other factors, for example, changes in screening.

Notwithstanding these arguments, the problem on what to advise women contemplating HRT can be problematic. Current advice recommends that the minimum effective dose of HRT should be used for the shortest duration, but for the treatment of menopausal symptoms the benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years (Joint Formulary Committee, 2010).

Psychological symptoms

Psychological symptoms include:

- depression
- mood changes and irritability, which may also be associated with other life changes occurring at this time
- exhaustion
- poor concentration and memory
- panic attacks
- lowered libido, which may be exacerbated by the above symptoms together with dyspareunia linked to lack of oestrogen and falling androgen levels.

The role of HRT in this area has not been clearly defined, although in several studies, surgical menopause has been associated with depression, indicating a correlation with oestrogen lack. Many women experience psychological symptoms around menopause, and although these may be associated with oestrogen deficiency, they may also result from the changes in family life that often occur around this time. Disturbance of sleep pattern and sleep deprivation, associated with menopause, are likely to contribute to the psychological symptoms. Many women find treatment with estradiol restores normal sleep and psychological problems are then reduced. Some of the mood changes will respond to counselling and psychotropic drugs. Treatment with oestrogens at high doses (patches of 100 µcg or implants of 50 mg) has also been shown to improve depression scores. If a progestogen is added into the regimen, then the results are less predictable since progestogen use is related to mood changes, particularly in women who have previously suffered from the pre-menstrual syndrome. Age negatively influences almost all sexual function domains in a significant manner.

HRT improves some aspects of sexual function during menopause, but it does not appear to improve the domains of desire and arousal. The lowered libido experienced during menopause is associated with reduced levels of circulating androgen resulting from ovarian failure. It has been demonstrated that subcutaneous implants of testosterone, 100 mg every 6 months, will increase the libido in a high proportion of patients.

Central nervous system

The relationship between oestrogen and neurodegenerative conditions, in particular, Alzheimer's disease (Mulnard et al., 2000), has received attention in the light of an observation that there is an increased incidence of the disease in older women. The development of plaques of amyloid-β, a protein that disrupts nerve cell connections in the brain, occurs more rapidly in the absence of oestrogen. This effect of amyloid-β production results in the symptoms of short-term memory loss and disorientation which occur in Alzheimer's disease (AD). Further studies are essential to clarify the relationship between HRT and Alzheimer's disease. There is some evidence that heavier women, who have higher free estradiol levels, exhibit better cognitive function in several domains. Such women may also have a greater clinical response when using exogenous oestrogen. It should also be noted that conjugated equine oestrogen is composed primarily of oestrone sulphate and this oestrogen has a much lower affinity for oestrogen receptors than oestradiol. Hence, the findings with respect to exogenous oestrogen and neurological function remain equivocal. The length of oestrogen deprivation before supplementation is also important as early administration of oestrogen for a period of several years may yet be found to be beneficial. Evidence is emerging that the progestogenic component in combined HRT is important and medroxyprogesterone acetate usage has been associated with negative cognitive outcomes. The potential of selective oestrogen receptor modulators (SERMs) as neuroprotectants has been evaluated in a breast cancer prevention trial which compared tamoxifen with raloxifene (Yaffe et al., 2001). Both agents were found to have similar effects on cognition. It is possible that HRT may have a neuroprotective effect under certain circumstances in some women and neuroimaging, for example, PIB (Pittsburgh compound B – a fluorescent agent). PET scanning may reveal effects not detectable using cognitive testing.

Case studies

Case 46.1

A 50-year-old patient has been on cyclical combined hormone replacement therapy for 6 months for troublesome hot flushes. Her periods were irregular before starting HRT. The hot flushes have resolved with this treatment and the withdrawal bleeds are acceptable, but she is struggling with the progestogenic side effects. A friend has told her to ask for the 'no-bleed' HRT as she thought this might suit her better.

Questions

1. What is the problem with considering a no-bleed preparation?
2. What other options could you suggest?

Answers

1. No-bleed preparations include continuous combined HRT and tibolone. If these are used in women before they become truly menopausal (rather than just peri-menopausal), they are associated with significant problems of unscheduled bleeding as the dose of hormone in the preparation is insufficient to override any residual ovarian activity. In women who start on HRT while still peri-menopausal, it can be difficult to know when they are truly menopausal. The recommendation therefore is that women should not take continuous combined HRT or tibolone until they are at least 12 months from their last menstrual period or are 54 years of age (when it is estimated that 80% of women will be post-menopausal).
2. Two options could be considered. Tridestra® could be used. This is a preparation where a 14-day course of combined estradiol valerate and medroxyprogesterone acetate is taken following a 70-day course of estradiol valerate. Seven days of inactive tablets follow during which the patient would be expected to have a withdrawal bleed. This means that the patient only experiences a bleed every 3 months rather than monthly. The other option would be to consider using the levonorgesterel IUS as the progestogen component of HRT together with either an oral or transdermal oestrogen preparation. This has the advantage of very few progestogenic side effects and the possibility that the patient will be rendered amenorrhoeic. If the levonorgesterel IUS is used, it should be replaced after 4 years rather than the usual 5 years when used for contraception or as a treatment for menorrhagia.

Case 46.2

An educated 57-year-old lady has been on oestrogen only HRT (Premarin® 1.25 mg) following a hysterectomy and bilateral oophorectomy for menstrual problems 10 years ago. She has mild, well-controlled hypertension. She has no personal or family history of breast disease, but her mother has osteoporosis. Her primary care doctor has suggested she should stop HRT because of concern about the long-term risks. The patient, however, is not keen, as when she tried to stop it in the past, she felt terrible.

Questions

1. What are the risks and also are there any benefits to her continuing with HRT?
2. How could she be managed?

Answers

1. She has a small increased risk of developing breast cancer, but there does not appear to be an increase in the risk of dying from breast cancer. HRT was started at the time her menopause, that is following a surgical menopause. Therefore, her risk of cardiovascular disease or stroke is not increased and may even be reduced. There may be a very small increase in the risk of venous thromboembolism, but this risk is greatest in the first year after starting HRT. There may be a reduction in the risk of developing colo-rectal cancer with HRT use. Treatment with HRT prevents osteoporosis but is not now recommended in the UK as first-line treatment for bone protection because of the balance of risk and benefit and the efficacy of other treatments such as bisphosphonates. For many women, the greatest benefit is the improved quality of life.
2. The lowest dose of HRT which relieves her menopausal symptoms, such as hot flushes, should be used. It would be sensible to halve the dose to start with and then consider a further slow reduction in dose. The patient's osteoporosis risk should be identified by reviewing diet, exercise, body mass index, etc., and bone densitometry. The risks and benefits should be discussed with the patient, taking into consideration both personal and family history. Once all the risk/benefit issues have been discussed and understood, the patient will then be in a position to make the final decision concerning treatment.

Case 46.3

A 43-year-old lady was started on cyclical HRT at the age of 37 when she was diagnosed with an early menopause after a 15-month period of amenorrhoea. She has no significant menopausal symptoms and regular light withdrawal bleeds. However, she has read that HRT should only be continued for 5 years and thinks she might stop HRT now.

Questions

1. Why should she be advised to continue HRT until the age of 50?
2. What advice would you give her regarding the dose and type of HRT?

Answers

1. Once a woman enters menopause, the fall in oestrogen levels increases the risk of cardiovascular disease and also increases bone loss causing a greater risk of osteoporotic fractures. The earlier the menopause, the greater the risk. Concern about breast cancer rates rising with increased HRT was derived from data in women over the average age of the natural menopause, that is, in their 50s, 60s and 70s. Therefore, it should not be extrapolated to women who have undergone early menopause. Women with an early menopause should be advised that any increase in the breast cancer risk only becomes important once HRT use continues beyond 50. In addition, the benefits of continuing HRT up to the age of 50 in terms of cardiovascular and bone health are significant.
2. Current advice is that the lowest dose of HRT to control menopausal symptoms should be used. This can result in the dose of HRT falling below the bone protective dose, and therefore a risk assessment for osteoporosis should be undertaken. This should include assessing lifestyle (dietary calcium, weight, weight-bearing exercise, etc.) in addition to a bone densitometry scan. This lady may wish to consider treatment with levonorgestrel IUS and oral or transdermal oestrogen as there may be a reduction in breast cancer risk associated with this combination when compared with standard cyclical HRT. This is because of limited systemic progestogen absorption. Cardiovascular well-being should be assessed, for example, family history, body mass index, blood pressure, lipids, aerobic exercise and improved where possible. This is especially important if following discussion of the risks and benefits, the patient still decided to stop HRT.

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Drugs in pregnancy and lactation 47

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Key points

Drugs in pregnancy

- Assess risk/benefit ratio for the mother-fetus pair.
- Avoid non-essential drugs.
- Where drug treatment is clinically indicated, select an effective agent with the best safety profile.
- Use the lowest effective dose for the shortest possible time.
- Provide timely and accurate counselling to help avoid unfounded maternal fears about drug safety that may otherwise result in non-adherence with drug therapy or unnecessary pregnancy termination.
- Use the statement 'avoid all drugs in the first trimester where possible' cautiously as drug exposure in the second and third trimesters may still result in fetal harm.
- Remember that the harmful effects of a drug on the fetus may differ depending on the trimester of exposure.

Drugs in lactation

- Avoid unnecessary use of drugs.
- Maternal therapy only rarely constitutes a reason to avoid breastfeeding.
- Assess the risk/benefit ratio for both mother and infant.
- Monitor the infant for unusual signs or symptoms.
- Avoid use of new drugs if there is a therapeutic equivalent for which data on use in lactation are available.

Drugs in pregnancy

The use of both prescription and over-the-counter drugs in pregnancy presents a number of challenges to those asked to provide advice to women either pre-conceptually or during pregnancy. This is in part due to the fact that no two cases are the same, and that each enquiry ideally requires an individual risk assessment that takes into account what is known about the drug and its effects on the developing fetus, as well as the woman's personal medical and family history. It is now well recognised that certain drugs, chemicals and other agents, readily cross the placenta and may act as teratogens, resulting in harm to the unborn child. Robust scientific human data on the effects of many of these drugs, particularly newer preparations, are, however, frequently lacking.

There is now a greater appreciation of the risks of drug use in pregnancy, and it is generally accepted that maternal pharmacotherapy should be avoided or minimised where possible. Nevertheless, it has been estimated that over 80% of expectant mothers take three or four drugs at some stage of pregnancy (Headley et al., 2004) with a significant number of women taking medication at the time their pregnancy is detected. Indications for drug use range from chronic illnesses such as epilepsy and depression to those commonly associated with pregnancy such as hypertension, urinary tract infections and gastro-intestinal complaints.

Approximately 2–3% of all live births are associated with a congenital anomaly. Although exogenous factors such as drugs may account for only 1–5% of these (affecting <0.2% of all live births), given that drug-associated malformations are largely preventable, they remain an important consideration.

Drugs as teratogens

A teratogen is defined as any agent that results in structural or functional abnormalities in the fetus, or in the child after birth, as a consequence of maternal exposure during pregnancy. Examples of drugs that are known to be human teratogens are shown in Box 47.1. The teratogenic mechanism for most drugs remains unclear, but may be due to the direct effects of the drug on the fetus and/or as a consequence of indirect physiological changes in the mother or fetus. Perhaps the best known, and most widely studied teratogen is thalodimide, a mild sedative

Box 47.1 Examples of drugs considered to be human teratogens

ACE inhibitors
Androgens
Carbamazepine
Carbimazole
Cytotoxics (some)
Danazol
Diethylstilboestrol
Ethanol
Lithium
Misoprostol
Penicillamine
Phenytoin
Tetracyclines
Thalidomide
Valproic acid
Vitamin A and derivatives, for example, isotretinoin
Warfarin

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that was widely marketed as a remedy for pregnancy-related nausea and vomiting. In 1961, thalidomide was withdrawn from the UK market following numerous reports of severe anatomical birth defects in infants of mothers who took the drug in early pregnancy. Whereas external congenital anomalies such as limb abnormalities, spina bifida and hydrocephalus may be obvious at birth, some defects may take many years to manifest clinically or be identified. Examples of delayed effects of teratogens are the behavioural and intellectual disorders associated with *in utero* alcohol exposure and the development of clear-cell vaginal cancer in young women following maternal intake of diethylstilboestrol, used first in the 1930s for the prevention of miscarriage and preterm delivery (Herbst et al., 1971).

Critical periods in human fetal development

The human gestation period is approximately 40 weeks from the first day of the last menstrual period (38 weeks' post-conception) and is conventionally divided into the first, second and third trimesters, each lasting 3 calendar months. Another method for classifying the stage of pregnancy is according to the stage of fetal development. This is a more useful approach when assessing the potential risks associated with drug use in pregnancy.

Pre-embryonic stage (weeks 0–2 post-conception)

The first two weeks post-conception are regarded as the pre-embryonic stage and describe the period up to implantation of the fertilised ovum. Teratogenic exposure during the pre-embryonic stage is thought to elicit an 'all-or-nothing' response, leading either to death of the embryo or complete recovery and normal development of the fetus. Fetal malformations following drug exposure during this period are therefore thought to be unlikely, except where the half-life of the drug is sufficient to extend exposure into the embryonic stage. A good example of the latter is isotretinoin and related vitamin A derivatives which have half-lives up to a week, and which when used systemically, for example, for the treatment of acne and psoriasis, are recognised teratogens (Nulman et al., 1998).

Embryonic stage (weeks 3-8 post-conception)

Organogenesis occurs predominantly during the embryonic stage and, with the exception of the central nervous system, eyes, teeth, external genitalia and ears, is complete by the end of the 10th week of pregnancy. Exposure to drugs during this critical period therefore represents the greatest risk of major birth defects. For this reason, women are often advised to avoid or minimise all drug use in the first trimester whenever possible. It is important to bear in mind however, that very few drugs are in fact proven teratogens and that exposure in the second and third trimesters may still result in fetal harm.

Fetal stage (weeks 9–38 post-conception)

During the fetal stage, the fetus continues to develop, grow and mature and, importantly, remains susceptible to some drug effects. This is especially true for the central nervous system, which can be damaged by exposure to certain drugs, for example, ethanol, at any stage of pregnancy. The external genitalia also continue to form from the seventh week until term, and consequently, danazol, which has weak androgenic properties, can cause virilisation of a female fetus if given in any trimester after the eighth week of pregnancy when the androgen receptors begin to form (Rosa, 1984).

Further examples include the angiotensin-converting enzyme (ACE) inhibitors, which if given in the second and third trimesters can result in fetal renal dysfunction and subsequent oligohydramnios, that is, reduced amniotic fluid volume (Sedman et al., 1995). The non-steroidal anti-inflammatory drugs (NSAIDs) are another important group of drugs that may cause problems specifically in the third trimester. These drugs inhibit prostaglandin synthesis in a dose-related fashion and, when given late in pregnancy, may result in premature closure of the fetal ductus arteriosus and fetal renal impairment (Koren et al., 2006). NSAIDs should therefore be avoided during the third trimester.

Principles of teratogenesis

In 1959, James Wilson, co-founder of The Teratology Society, proposed several principles of teratogenesis that have since been expanded and modified but remain fundamental in assessing whether a drug or chemical exposure during pregnancy is likely to be associated with reproductive or developmental toxicity. A basic understanding of these factors is essential to both the interpretation of preclinical (animal) reproductive toxicity studies and to enable accurate risk assessment in clinical practice. A subset of Wilson's principles are discussed as follows.

Timing of exposure

The stage of pregnancy at which a drug exposure occurs is key to determining the likelihood, severity or nature of any adverse effect on the fetus. Risk both between and within trimesters may be variable. For example, folic acid antagonists, for example, trimethoprim, are associated with an increased risk of neural tube defects if exposure occurs before neural tube closure (third to fourth week post-conception), but not after this period (Hernandez-Diaz et al., 2001). It has also been suggested that trimethoprim should be avoided after 32 weeks' gestation in view of the theoretical risk of severe jaundice in the neonate as a result of bilirubin displacement from protein binding, although clinical evidence to support this is lacking (Dunn, 1964). Unfortunately, the precise period of teratogenic risk is known for very few substances. One drug for which this period has been established is thalidomide, where exposure between days 20 and 36 post-conception is associated with a high risk of congenital malformation (Lenz, 1988; Newman, 1986).

Drug dose

A threshold dose above which drug-induced malformations are more likely to occur has now been demonstrated for certain teratogenic compounds, although for most a 'safe dose'

has not been conclusively determined. The likelihood of a dose relationship underlies the recommendation to use the lowest effective dose in pregnancy. For this reason, more frequent monitoring of drug levels may be recommended for certain drugs during pregnancy.

Species

Teratogenicity of a drug may be species dependent. Interestingly, preclinical thalidomide studies in mice and rats did not result in congenital malformation in the offspring (Breitkreutz and Anderson, 2008; Miller et al., 2009; Vorhees et al., 2001). Birth defects or other adverse reproductive outcomes observed in animal studies cannot therefore be simply extrapolated to the human situation. Further, the drug dose and route of administration used in early animal studies may not be comparable to clinical use in humans.

Genotype and environmental interaction

Not all fetuses exposed to known teratogenic drugs show evidence of having been affected *in utero*. It remains undetermined as to whether this variable susceptibility to teratogenic drugs is a result of genetic differences in the exposed mothers, the fetal genotype, modifying environmental factors or a combination of all three. Malformations are reported to occur in only 20–50% of infants born to mothers exposed to thalidomide during the period of greatest risk for embryopathy, that is, days 20–36 post-fertilisation (Lenz, 1966; Newman, 1985). Similarly, maternal treatment with systemic isotretinoin during the first trimester results in fetal malformation in only 18–35% of the live born infants, with a further 30% of children exhibiting developmental delay in the absence of physical deformity (Benke, 1984; Braun et al., 1984; Hill, 1984).

Pharmacological effect

Pharmacological effects on the fetus are by far the most common drug effects during pregnancy, and the consequences are often minor and reversible compared to the idiosyncratic effects that can lead to major irreversible anomalies. Pharmacological effects are usually dose related and to some extent predictable. Drugs may adversely affect the fetus via effects on the maternal circulation or they may cross the placenta and exert a direct pharmacological effect on the fetus. Equally, drugs are sometimes administered to pregnant women in order to treat fetal disorders; for example, flecainide has been used to resolve fetal tachycardia.

The neonate can also be adversely affected by maternal drug therapy (see Table 47.1). It is generally only at birth that signs of fetal distress are observed due to *in utero* drug exposure or the effects of abrupt discontinuation of the maternal drug supply. The capacity of the neonate to eliminate drugs is reduced, and this can result in significant accumulation of some drugs, leading to toxicity. Neonatal withdrawal effects may require treatment.

Idiosyncratic drug effects in the fetus and neonate are possible but occur rarely compared with pharmacological effects.

Table 47.1 Examples of drugs with pharmacological effects on the fetus or neonate (adapted from Schaefer et al., 2007)

Drug	Possible adverse pharmacological effect	Notes
ACE inhibitors	Fetal and neonatal hypoxia, hypotension, renal dysfunction, oligohydramnios and intra-uterine growth retardation	Monitor fetus if long-term therapy in the second or third trimester
β-Blockers, for example, atenolol	Neonatal bradycardia, hypotension and hyperglycaemia	Neonatal symptoms are usually mild and improve within 48 h. No long-term effects
Benzodiazepines	'Floppy infant syndrome' Withdrawal reactions	Risk if regular use in third trimester Neonatal observation recommended
Corticosteroid (high dose)	Fetal adrenal suppression	Dependent on dose and treatment interval
NSAID	Premature closure of the ductus arteriosus (affecting fetal circulation) and fetal renal impairment (decreased urine output)	Avoid repeated use after week 28. If unavoidable, fetal circulation monitored regularly
Opioids	Neonatal withdrawal symptoms Respiratory depression	Risk if used long-term Risk if used near term
Phenothiazines	Neonatal withdrawal and transient extrapyramidal symptoms	Observation for at least 48 h. Symptoms may last for several weeks
Tricyclic and SSRI antidepressants	Neonatal withdrawal symptoms	Risk if used long-term and/or near term. Observation for at least 48 h

Maternal pharmacokinetic changes

There are a number of maternal changes which occur during pregnancy and are summarised in Table 47.2.

Absorption

Gastric and intestinal emptying time increases by 30–40% in the second and third trimesters (Pavek et al., 2009) and could be important in delaying absorption and time to onset of action for some drugs (Loebstein et al., 1997). There is also a reduction in gastric acid secretion in the first and second trimesters and an increase in mucus secretion. As a consequence of the increase in gastric pH, the ionisation, and hence absorption, of weak acids and bases can be affected.

Cardiac output and respiratory volume increase during pregnancy leading to hyperventilation and increased pulmonary blood perfusion. These changes cause higher pulmonary absorption of anaesthetics, bronchodilators, pollutants, cigarette smoke and other volatile drugs.

Distribution

The volume of distribution of drugs may be altered because of an increase of up to 50% in blood (plasma) volume and a 30% increase in cardiac output. Renal blood flow increases by up to 50% at the end of the first trimester and uterine blood flow increases and peaks at term (36–42 L/h). There is also a mean increase of 8 L in body water (60% to placenta, fetus and amniotic fluid and 40% to maternal tissues). As a consequence, there may be increased dosage requirements for some drugs to achieve the same therapeutic effect, provided these effects are not offset by other pharmacokinetic changes. Both the total plasma and the free-drug concentrations of phenytoin, carbamazepine and valproic acid decrease during pregnancy, but the free-drug fraction (ratio of free to total plasma concentration) may increase (Pavek et al., 2009).

Table 47.2 Summary of pharmacokinetic changes during pregnancy (adapted from Schaefer et al., 2007)

Absorption	Change during pregnancy
Gastro-intestinal motility	↓
Lung function	↑
Skin blood circulation	↑
Distribution	
Plasma volume	↑
Body water	↑
Plasma protein	↓
Fat deposition	↑
Metabolism	
Liver activity	↑↓
Excretion	
Glomerular filtration	↑

Protein binding

Albumin is the main plasma protein responsible for binding acidic drugs such as phenytoin and salicylates, whilst α_1-acid glycoprotein predominantly binds basic drugs, including β-blockers and opioid analgesics. As pregnancy progresses, the plasma volume increases at a greater rate than the increase in albumin which results in hypoalbuminaemia. In addition, steroid and placental hormones occupy the protein-binding sites. This leads to an increase in the fraction of unbound drug. Clinical effect is related to the concentration of unbound drug, which usually remains unchanged even though the total (bound plus unbound) plasma concentration is decreased. Thus, a fall in the total plasma concentration does not usually require an increase in dose. The α_1-acid glycoprotein concentrations remain the same as those in non-pregnancy.

Phenytoin is bound to albumin and exhibits the effects described earlier, but the situation is further complicated by increased hepatic metabolism that may necessitate a dose increase. Consequently, therapy can only be reliably guided by clinical assessment or measurement of unbound rather than total plasma concentration.

Metabolism

The metabolic activity of cytochrome P450 isoenzymes CYP3A4, CYP2D6, CYP 2A6 and CYP 2C9 and uridine 5′-diphosphate glucuronosyltransferase (UGT) isoenzymes (UGT1a1, UGT1A4 and UGT2B7) is increased during pregnancy. Drugs metabolised by these isoenzymes may therefore require dose adjustment. This may decrease the amount of the drug available for transfer across the placenta and thereby influence fetal exposure. In contrast, the metabolic activity of CYP1A2 and CYP2C19 is decreased during pregnancy and drugs metabolised by these isoenzymes may need dose reduction to minimise toxicity (see Table 47.3).

In general, the effects on individual drugs are inconsistent and difficult to predict, but knowledge of the effect of pregnancy on isoenzymes may inform decisions about possible monitoring and/or dose alterations.

Excretion

Within the first few weeks of pregnancy, the glomerular filtration rate (GFR) increases by approximately 50%. Consequently, those drugs which are excreted primarily unchanged by the kidneys, for example, lithium, digoxin and penicillin, show enhanced elimination and lower steady-state concentrations. The following drugs have shown pregnancy-induced increases of 20–65% on their renal elimination (Anderson, 2005):

- Ampicillin
- Cefuroxime
- Ceftazidime
- Cefazolin
- Pipericillin
- Atenolol

Table 47.3 Summary of pregnancy-induced effects on hepatic metabolism of some drugs (adapted from Anderson, 2005)

Isoenzyme	Drugs/probes	Effect on clearance		
		First trimester	Second trimester	Third trimester
CYP1A2	Caffeine	↓ 33%	↓ 50%	↓ 65%
CYP2A6	Nicotine	ND	↑ 54% (combined data)	
CYP2C9	Phenytoin	No effect	No effect	↑ 20%
CYP2C19	Proguanil	ND	↓ 50%	↓ 50%
CYP2D6	Dextromethorphan[a] Metoprolol	ND	ND	↑ 50%
CYP3A4	Cortisol[a] Nifedipine	ND	ND	↑ Variable[b]
UGT1A4	Lamotrigine monotherapy polytherapy	↑ 200% ↑ 65%	↑ 200% ↑ 65%	↑ 300% ↑ 90%
UGT2B7 (limited data)	Morphine	ND	ND	↑ Variable[b]

ND, not detectable.
[a]Dextromethorphan and cortisol used as probes of CYP2D6 and CYP3A4 activity.
[b]Extent variable depending on the drug studied.

- Sotalol
- Digoxin
- Lithium
- Dalteparin sodium
- Enoxaparin sodium

Fetal-placental transfer

Most drugs diffuse easily across the placenta and thus enter the fetal circulation to some extent. In general, the ratio fetal:maternal drug concentration is less than 1. Drugs differ in the extent to which they bind to fetal and maternal proteins. For example, fetal and newborn plasma proteins appear to bind ampicillin and benzylpenicillin with less affinity and salicylates with greater affinity, than maternal proteins. Maternal albumin gradually decreases during pregnancy and fetal albumin concentrations increase, so different fetal: maternal albumin concentrations occur at different stages of pregnancy. The degree of protein binding of any drug is an important determinant of its movement across the placenta. Drugs which are highly protein bound tend to achieve higher maternal and lower fetal concentrations. Drugs with very large molecular weights such as insulin and heparin have negligible transfer. Lipophilic, un-ionised drugs cross the placenta more easily than polar drugs, and weakly basic drugs may become 'trapped' in the fetal circulation due to the slightly lower pH compared with maternal plasma. Some other factors such as enzymes or drug efflux transporters in the placenta may facilitate or restrict the transfer of a drug to the fetus.

Drug dosing in pregnancy

As a general principle, the dose of a drug given at any stage of pregnancy should be as low as possible to minimise potential toxic effects to the fetus. Drug therapy that is considered essential can be tapered to the lowest effective dose either before conception (ideally) or at the time the pregnancy is diagnosed. Where drug exposure during the third trimester is predicted to have an adverse effect on the neonate postpartum, consideration may be given to slowly reducing the dose towards term to minimise the risks to the baby. Such decisions are, however, not always straightforward. Recommendations to wean an expectant mother off antidepressants and antipsychotics to reduce the likelihood of neonatal withdrawal syndrome (characterised by jitteriness, altered muscle tone, poor feeding and irritability) and, in the case of the SSRIs, avoid the possible increased risk of persistent pulmonary hypertension of the newborn (PPHN) are now being challenged. Not only are there insufficient data to conclusively demonstrate neonatal benefit or an optimal time of weaning, but also the increased risk of psychiatric problems and relapse in the immediate postpartum period needs to be taken into account.

Many physiological changes occur during pregnancy which may affect the way the body handles drugs. Knowledge of these changes can allow some prediction of the impact on pharmacotherapy while remaining aware that there is variability in the extent of these changes during the pregnancy, and high inter-individual variability. The need for changes in dosages is influenced by whether the drug is excreted unchanged by the kidneys or which metabolic isoenzymes are involved in its elimination. Women taking drugs with enhanced clearance

and for which a good correlation between plasma levels and therapeutic effect exist, should have their plasma concentrations closely monitored and dose adjusted to reduce the risk of suboptimal therapy, for example, phenytoin, carbamazepine, lithium and digoxin. Similarly, highly protein-bound drugs may require free-drug concentration monitoring. However, there is no clear guidance for adjusting doses during pregnancy, and for most drugs, the concentration of free drug, and therefore the effect of that drug, is unchanged.

Pregnancy itself can cause a temporary worsening or improvement of some diseases and in that way influence drug dosages.

Drug selection in pregnancy

Although there are few, if any, drugs for which safe use in pregnancy can be absolutely assured, only a handful of drugs in current clinical use have been conclusively shown to be teratogenic. In general, drugs that have been used extensively in pregnant women without apparent problems are recommended in preference to new drugs for which there is less experience of use. For example, methyldopa is used rarely to treat hypertension in the non-pregnant state but has historically been preferred in pregnancy because of a long history of safe use (Schaefer et al., 2007). However, older drugs may be less effective in terms of controlling maternal illness and are often associated with an increased side-effect risk profile.

In most cases, the decision as to whether to commence or continue with a medication in pregnancy will depend on the risk–benefit analysis for that specific mother–infant pair. A frequent error made by health professionals is to apply the U.S. Food and Drug Administration (FDA) pregnancy risk categories (A (*no demonstrable risk*), B, C, D and X (*teratogenic agents that are considered to be completely contraindicated in pregnancy*) when considering whether or not to prescribe a drug in pregnancy. It is now widely accepted that these categories are oversimplified and are of little practical help in a clinical setting. The FDA has proposed that the existing categories be replaced with more detailed information sheets containing a summary of the fetal risk and the additional maternal factors that need to be taken into consideration. Importantly, the need for a detailed section discussing the available data including observed human versus animal data, the study design, dose exposure, and reported congenital malformations and/or adverse events has been emphasised (see http://www.fda.gov for up-to-date information).

It is worth noting that standard literature sources often contain unhelpful information such as 'do not use in pregnancy unless the benefits outweigh the risks'. This is understandable from a medico-legal point of view but offers little in terms of risk assessment. The primary literature is frequently inadequate because ethical and legal restraints mean that randomised controlled trials are rarely undertaken in pregnant women. Often, the only information that is available is confined to retrospective studies, voluntary reporting schemes and/or animal studies. The rate of anomalies in retrospective studies and voluntary reporting databases may be erroneously elevated due to preferential reporting of abnormal outcomes. Individual case reports are also difficult to interpret as the denominator of drug exposure is unknown, and an abnormal outcome may be coincidental to the drug exposure. More recently, prospective controlled trials have been utilised where the pregnancy outcomes of a defined cohort of women exposed to the drug are compared with outcomes of a matched control group. Complete follow-up of each pregnancy and post-natal monitoring is an essential feature of this type of investigation.

Pre-conception advice

Drug use during the first trimester, in particular, the embryonic stage, carries the greatest risk of malformation as this is when the fetal organs are being formed. Ideally, all unnecessary drug therapy should be discontinued prior to conception. However, inadvertent drug exposure frequently occurs, as approximately half of all pregnancies are unplanned. It is thus critical to make careful drug choices when prescribing for women of reproductive potential.

Women with chronic illnesses requiring drug treatment should be offered specialist counselling before conception, and the options explored to reduce or change drug therapy to a safer agent. Epilepsy is an example, in which, if continued drug treatment is necessary, attempts are made to stabilise treatment with a single drug at the lowest effective dose. It is also important to note that many pregnant women become less adherent to their drug therapy out of concern about possible harm to their infant. In many cases, such as asthma, inflammatory bowel disease, epilepsy, inadequate treatment of the underlying disease may be more detrimental to the mother–fetus pair than the drugs used to treat the condition. It is thus essential that women of reproductive potential are given clear and accurate information so that unrealistic fears about the risks to their baby do not result in unnecessary pregnancy termination or disease relapse.

All women planning a pregnancy should be offered general advice to minimise the risk of congenital anomalies. This includes avoidance of recreational drugs, 'natural' or herbal remedies, alcohol, smoking, vitamin A products, minimisation of caffeine consumption and beginning daily supplementation with at least 400 μcg of folic acid to reduce the risk of neural tube defects. It is recommended that the daily dose of folic acid be increased to around 4–5 mg daily in women who have epilepsy or who have had a previous child with a neural tube defect. Some infectious diseases may carry important fetal consequences if contracted during pregnancy. For example, rubella infection in the first 20 weeks of pregnancy is associated with an increased risk of miscarriage and a syndrome comprising problems such as deafness, cardiac defects and mental retardation in more than 20% of pregnancies. Women who lack immunity to rubella should be immunised prior to conception.

Post-conception advice

It is important to draw distinction between advice given to women pre-conceptually and that provided to a pregnant woman who has already been exposed to a drug. In the former setting, it may be recommended that an alternative

preparation be considered or that a drug treatment be stopped where clinically appropriate. This advice often hinges on the lack of definitive safety data and does not automatically translate to exposure to that drug in pregnancy being an indication for discontinuing the drug, additional fetal monitoring or termination of the pregnancy on the basis of the exposure. Any change to the woman's medication should be based on a careful and individual risk assessment and include a discussion with the woman to provide her with accurate up-to-date evidence-based advice. In many such cases, the woman can be reassured that a normal baby is the most likely outcome, or where appropriate be offered additional prenatal investigation to screen for congenital malformation where the risk to fetus is considered to be significant.

Teratology Information Services and Pregnancy Registries

It is difficult to keep up to date with the published literature. There is an increasing need for summary documents that include and critically appraise all available data, and which enable health care providers to have a balanced and informed discussion with patients regarding the risks and benefits of a certain therapy in pregnancy. This is evidenced by the current debate surrounding the teratogenic potential of various antidepressants with conflicting opinion even amongst experts in the field.

Teratology information services (TISs) have been established in several countries across the world and provide evidence-based, up-to-date information and individual case-based risk assessments. In addition to reviewing published literature on drugs, teratology services also have access to specialist online databases and discussion forums. A number routinely collect pregnancy outcome data on the women about whom they receive an enquiry, to enable surveillance for potential teratogens.

For some new drugs, pregnancy registries have been initiated that record all reported drug exposures and follow up the outcome of the pregnancy. These registries are cumulative and work on the basis that specific anomalies would be identified relatively quickly and that there will eventually be sufficient statistical power to detect the magnitude of any increased risk relative to the general population. These registries may be held by a TIS, or by independent groups with an interest in a defined area. The 2009 A/H1N1 influenza pandemic provided an example of teratology services across the globe responding to the urgent need for safety data by establishing registries on antiviral and pandemic vaccine exposure during the pandemic.

Drugs in lactation

Breast milk is the best form of nutrition for young infants. It provides all the energy and nutrients required for the first 6 months of life. The World Health Organization (WHO, 2001) and the United Nations Children's Fund (UNICEF) recommend exclusive breastfeeding for this period. Benefits of breastfeeding include protection of the infant against gastric, respiratory and urinary tract infections (Kramer and Kakuma, 2002), and reduction in rates of obesity (Horta et al., 2007), juvenile-onset diabetes (Horta et al., 2007) and atopic disease (Fewtrell, 2004). Adults who were breastfed as infants often have lower blood pressure and lower cholesterol levels (Horta et al., 2007). Maternal benefits include reduced risk of developing pre-menopausal breast cancer and delayed resumption of menstrual cycle. Breastfeeding also strengthens the mother–infant bond.

There are few contraindications to breastfeeding, although maternal HIV infection in developed countries is a notable exception. The percentage of women exclusively breastfeeding their infants after 6 months is often less than 20% (Scott et al., 2006). Reasons for early discontinuation of breastfeeding include return to work, concerns about inadequate lactation or safety of drug use.

Breastfeeding mothers frequently require treatment with prescription medicines or may self-medicate with over-the-counter preparations, nutritional supplements or herbal medicines. It is important for health professionals to understand the principles of safe use of medications during lactation in order to provide appropriate advice.

There are two main goals to consider when formulating advice for nursing mothers. These are to protect the infant from maternal drug-related adverse effects and to allow, whenever possible, necessary maternal medication (Berlin et al., 2009).

Transfer of drugs into breast milk

Most drugs pass into breast milk to some degree although transfer is usually low. The drug 'dose' ingested by the infant via breast milk only rarely causes adverse effects. Examples of adverse effects observed in breastfed infants exposed to medication via breast milk are given in Table 47.4, although not all of these are proven to be directly due to the drug ingested via breast milk.

Table 47.4 Adverse reactions reported in breastfed infants

Atenolol	Bradycardia, cyanosis, hypotension
Ciprofloxacin	Pseudomembranous colitis
Codeine	Death
Dapsone	Haemolytic anaemia
Diazepam	Lethargy, sedation, poor suckling
Doxepin	Sedation and respiratory arrest
Erythromycin	Pyloric stenosis
Fluoxetine	Colic, irritability, sedation
Indometacin	Seizures
Lithium	T-wave abnormalities
Naproxen	Prolonged bleeding, haemorrhage, anaemia
Phenytoin	Methaemoglobinaemia

Almost all drugs enter milk by passive diffusion of un-ionised, unbound drug through the lipid membranes of the alveolar cells of the breast, according to the pH partitioning theory. Several factors influence the rate and extent of passive diffusion. These include maternal plasma level, physiological differences between plasma and milk and the physicochemical properties of the drug. Differences in composition between blood and milk determine which physicochemical characteristics influence diffusion.

Milk differs from blood in that it has a lower pH (7.2 vs. 7.4), less buffering capacity and higher fat content. The following drug parameters affect the extent of transfer into milk:

- pK_a. This is a measure of the fraction of the drug that is ionised at a given pH, for example, physiological pH. Highly ionised drugs tend not to concentrate in milk. For basic drugs, for example, erythromycin, a greater fraction will be ionised at an acidic pH, so the milk compartment will tend to 'trap' weak bases. In contrast, acidic drugs, for example, penicillins, are more ionised at higher pH values and will be 'trapped' in the plasma compartment. Drugs with higher pK_a values generally have higher milk/plasma ratios.
- *Protein binding*. Drugs that are highly bound to plasma proteins, for example, warfarin, are likely to be relatively retained in maternal plasma because there is a lower total protein content in the milk. High protein binding essentially restricts the drug to the plasma compartment as only the free fraction of the drug crosses the biological membrane. Milk concentrations of highly protein-bound drugs are usually low.
- *Lipophilicity*. The alveolar epithelium of the breast is a lipid barrier. Transfer of water-soluble drugs and ions is inhibited by this barrier. CNS active drugs usually have the characteristics required to pass into milk.
- *Molecular weight*. Drugs with low molecular weights (<200) readily pass into milk through small pores in the cell walls of alveolar cells. Drugs with higher molecular weights cross cell membranes by dissolving in the lipid layer which may substantially reduce milk concentrations. Proteins such as heparin or insulin with very large molecular weights of > 6000 are virtually excluded from milk.

The profile of a drug that passes minimally into milk would therefore be an acidic drug that is highly protein bound and has low to moderate lipophilicity, for example, most NSAIDs. In contrast, a weakly basic drug that has low plasma protein binding and is relatively lipophilic will achieve higher concentrations in the milk compartment, for example, sotalol.

In the first few days of life, large gaps exist between the alveolar cells. These permit enhanced passage of drugs into milk. By the end of the first week, these gaps close under the influence of prolactin (Lawrence and Lawrence, 2011). There is greater passage of drugs into colostrum (early milk) than in mature milk as the former contains more protein and less fat. There is also some variation in fat and protein content of milk between the beginning and end of a feed, but these changes have less influence on drug passage than the physicochemical properties of the drug.

Another method by which a drug may enter milk is by a pumping system whereby energy is used to effect transfer into milk. The most important example is iodides which pass into milk in high concentrations (Hale, 2010).

Milk to plasma concentration ratio

Several methods have been proposed to determine the amount of drug transferred to breast milk. The milk to plasma (M/P) ratio is often used as a measure of the extent of drug transfer into breast milk. It is usually obtained from case reports or small clinical studies and may be based on paired concentrations or full area under the concentration–time curve (AUC) analysis. M/P ratios that are based on a pair of milk and plasma samples collected simultaneously may be inaccurate as they assume that the concentrations of drug in milk and plasma are in parallel, which may not be the case. It is better to collect multiple samples of plasma and milk across a dosing interval or until the drug is cleared from both phases after a single dose, for determination of an M/P ratio based on the respective AUCs (M/P_{AUC}). Figure 47.1 demonstrates the markedly different estimates of M/P ratio that can be obtained via both sampling methods. The true M/P ratio may vary significantly during the same episode of breastfeeding.

If human-derived M/P ratios are lacking for a particular drug, it may be possible to predict the extent of transfer using known physicochemical properties, for example, pK_a, and a published predictive model (Atkinson and Begg, 1990; Begg et al., 1992). M/P ratios obtained from animal studies should not be used for clinical decision making, as they may not correlate well with human M/P ratios.

Studies in humans demonstrate that most drugs have an M/P ratio less than 1.0, with the range of reported ratios being from around 0.1 to 5.0. It is often thought that drugs with high M/P ratios (e.g. 5.0) are unsafe because the concentration in milk exceeds that in plasma, while those with low ratios (<1.0) are believed to be safe. This is not always the case as the M/P ratio often fails to correlate with the 'dose' of drug the infant

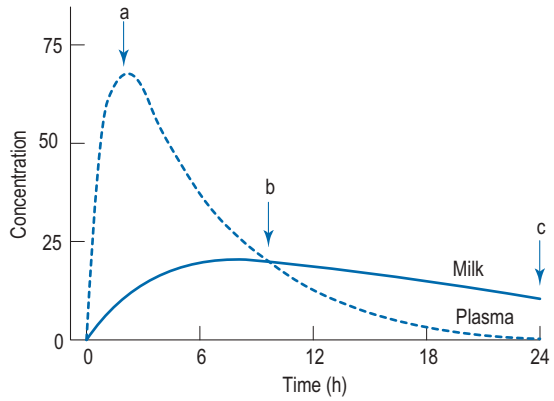


Fig. 47.1 Diagrammatic representation of a drug concentration–time profile in the maternal plasma and milk phases after a single oral dose. The points a, b and c illustrate simultaneous sampling times from both phases. Sampling at 'a' would yield an estimated M/P value of 0.2, at 'b' a value of 1.0, and at 'c' a value of 9.3. All can be misleading. The true M/P ratio calculated by the AUC method is 1.2 when extrapolated to infinity.

ingests via milk. The amount of drug transferred into milk is principally determined by the maternal plasma level. Thus, even where the *M*/*P* ratio is high, if the maternal plasma level is low, drug transfer is still low. Therefore, the *M*/*P* ratio must never be used as the sole measure of drug safety in breastfeeding. However, it can be used to estimate the 'dose' ingested via milk, which is a better predictor of safety.

Calculating the infant 'dose' ingested via milk

Infant plasma drug levels are the most accurate indicator of drug exposure, but these are seldom available.

When using quantitative data from milk analyses, the most accurate estimation of the infant 'dose' is from studies in which the milk is collected over a complete dose interval at steady state and the total dose is calculated (Fig. 47.2). Unfortunately, these studies are seldom performed. Therefore, information must be obtained from less than ideal conditions.

If the *M*/*P* ratio is known from published studies, the likely infant dose (D_{inf}) can be calculated as follows, with some assumptions:

$$D_{inf} = \mathrm{Cp}_{mat} \times M/P \times V_{milk}$$

where Cp_{mat} is the average maternal plasma concentration. M/P_{AUC} is used in preference to a ratio based on paired concentrations when available, but this is seldom the case. The volume of milk ingested (V_{milk}) is not known but is generally assumed to be around 150 mL of milk per kilogram of body weight per day. The above equation simplifies if the actual milk concentration data are available:

$$D_{inf} = C_{milk} \times V_{milk}$$

The likely infant plasma drug concentration (Cp_{inf}) can be calculated by:

$$\mathrm{Cp}_{inf} = F \times D_{inf} / \mathrm{Cl}_{inf}$$

where *F* is oral availability and Cl_{inf} is the infant clearance. Unfortunately, neither *F* nor Cl_{inf} is known accurately for infants, so estimation of the likely steady-state average plasma drug concentration will be very approximate. Weight-adjusted Cl_{inf} values, that is, L/h/kg, are often significantly less than adult values in the early stages of life (Table 47.5).

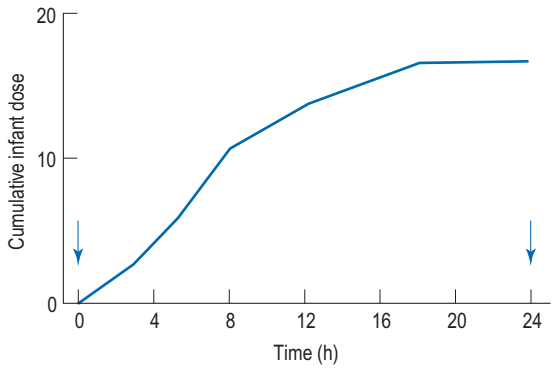


Fig. 47.2 The cumulative dose received by the infant is plotted against time. The arrows represent the maternal dose times. This type of study is undertaken by the mother expressing all the milk, from both breasts, at usual feeding times. An aliquot of milk is taken and assayed for the drug. The volume of milk is measured and the total amount of drug at each time is calculated as the product of concentration and volume. This type of study must be undertaken at steady state.

Given the difficulty in estimating infant plasma drug concentrations, the relative infant dose, for example, compared with a therapeutic infant dose, is often used as a surrogate of exposure. To give some basis for comparison, the likely infant dose from milk can be compared with an infant therapeutic dose. This is reasonable for drugs such as paracetamol that are usually administered to infants but is unsuitable for drugs such as antidepressants that are not. In the absence of a clearly defined range of infant doses, the weight-adjusted maternal dose expressed as a percentage (% dose) is widely used to indicate infant drug exposure.

$$\text{Relative infant dose (RID)} = \frac{\text{Dose in infant via milk } [D_{inf}\,(\text{mg/kg/day})]}{\text{Dose in mother } [D_{mat}\,(\text{mg/kg/day})]} \times 100$$

For the great majority of drugs, this calculation yields infant doses in the order of 0.1–5.0% of the weight-adjusted maternal dose expressed as a percentage (% dose). It is generally thought that relative infant dose values of less than 10% of the maternal dose are probably safe. However, the inherent toxicity of the drug should be taken into account when using this figure.

To calculate the daily infant drug intake via milk, the standard milk intake of 150 mL/kg/day is multiplied by the concentration of the medication in milk:

Estimated daily infant intake = Drug concentration in milk (μcg/L) × 0.15/infant weight (kg)

Some authors use the peak concentration in milk to indicate the maximum infant intake.

Variability

To complicate matters further, there will be significant variability between and within individuals in the values used to estimate infant exposure (i.e. D_{inf}, *F*, Cl_{inf}, where D_{inf} is itself a function of the estimated parameters Cp_{mat}, *M*/*P*, volume of milk). Some of this variability will change over time due to developing organ function in the maturing baby and part will

Table 47.5 Approximate drug clearance by age as percentage of maternal value (Begg, 2000)

24–28 weeks' post-conceptual age	5%
28–34 weeks' post-conceptual age	10%
34–40 weeks' post-conceptual age	33%
40–44 weeks' post-conceptual age	50%
44–68 weeks' post-conceptual age	66%
Over 68 weeks' post-conceptual age	100%

be unexplained variability. In addition to this pharmacokinetic variability, there will be variability in response of the infant to any given concentration of the drug. It is fortunate that most drugs seem to fall readily into safe (RID <10%) based on expected exposure. However, care should be taken when using these values to assess drug safety in lactation, when variability in the estimates of the parameters used may impact on the accuracy of prediction of their safety. This is especially true for those circumstances when initial estimates of these parameters are less precise, for example, in neonates.

Recently, attention has been focused on the possible role of pharmacogenetic factors in affecting the safety of breastfed infants exposed to drugs via milk (Madadi et al., 2009). Sedation (and one death) occurred in infants of mothers with rare genotypes of cytochrome P450 2D6 leading to ultra-rapid metabolism of codeine to morphine. The incidence of these genotypes varies amongst different populations. The overall percentage of Western Europeans with the CYP2D6 ultra-rapid metaboliser phenotype is 5.4% (Ingelman-Sundberg, 2005). Higher percentages have been reported in populations from northeast Africa and the Middle East.

Assessing the risk to the infant

Many factors must be considered when assessing the risk of maternal drug therapy to the breastfeeding infant (Box 47.2).

Inherent toxicity of the drug will be a main factor in determining infant safety. Thus, antineoplastic drugs, radionuclides and iodine containing compounds would be of concern. Multiple maternal therapy with drugs with similar side-effect profiles, for example, psychotropic drugs or anticonvulsants is likely to increase the risk to the infant. Oral bioavailability is an indicator of the drug's ability to reach the systemic circulation after oral administration. Drugs with a low oral bioavailability are either poorly absorbed from the gastro-intestinal tract, broken down in the gut or undergo extensive 'first pass' metabolism in the liver before entering plasma.

The presence of active metabolites, for example, desmethyldiazepam, may prolong infant drug exposure and lead to drug accumulation, especially where drug clearance is low such as in the neonatal period. Similarly, drugs with long half-lives, for example, fluoxetine, may be problematic at this time. Drug clearance by the infant does not reach adult values until 6–7 months (Table 47.5). A premature infant of 30 weeks' gestational age has a drug clearance value of about 10% of the maternal value. It is important to distinguish between gestational age and time after delivery. A 2-week-old infant born at 28 weeks will have a gestational age of 30 weeks.

Box 47.2 Factors affecting infant risk from maternal therapy

- Drug adverse reaction profile
- Relative infant dose (RID)
- Oral bioavailability
- Active metabolites
- Half-life
- Gestational age of the infant
- Full maternal drug regimen
- Pharmacogenetic factors

The maternal drug regimen can affect infant risk. Single doses or short courses seldom present problems, whereas chronic therapy can be problematic. Topical or inhalation therapy usually results in much lower plasma drug levels and therefore lower passage into milk. Multiple maternal medications increase the risk to the infant.

Reducing risk to the breastfed infant

A number of strategies may be adopted to reduce the risk of drug-related side effects in the breastfed infant. One technique that has been recommended for reducing infant exposure is to give the maternal dose immediately after the infant has been fed with the aim of avoiding feeding at peak milk concentrations. However, this is often impractical, especially where young infants are feeding frequently up to 2 hourly. In addition, accurate data on times of peak levels in milk are often unavailable, and it cannot be assumed that times of peak milk levels mirror those in plasma. This technique should be used selectively, that is, where the drug has a short half-life and where peak and trough levels are predictable, for example, antibiotics, anaesthetics.

Where a single dose of a drug known to be hazardous is given to a breastfeeding mother, for example, a radiopharmaceutical, it will usually be possible to resume breastfeeding after a suitable washout period, calculated as five times the half-life. Where the half-life is very long, the washout period necessary to avoid hazardous exposure to the infant may exceed the period of sustainable lactation.

Breastfeeding mothers should be advised to avoid self-medication. Where drug use is clearly indicated, the lowest effective dose should be used for the shortest possible time. Use of topical therapy such as eye/nasal drops for hay fever would reduce drug exposure in comparison to oral antihistamines.

The maternal regimen should be simplified wherever possible. A review of therapy before delivery will help to reduce risks to the neonate. New drugs are best avoided if a therapeutic equivalent is available for which data on safe use in lactation exists. All infants exposed to drugs via breast milk should be monitored for any untoward effects. Measures to ensure the safety of the breastfed infant are summarised in Box 47.3. Some commonly used drugs thought to be safe to use in mothers of full-term healthy infants are listed in Table 47.6.

Special situations

Neonates and premature infants

Neonates and especially premature infants are at greater risk of developing adverse effects after exposure to drugs via breast milk. Gastric emptying time is significantly prolonged and, in some cases, may alter absorption kinetics. Protein binding is decreased and values for total body water are higher than for adults. Renal function is limited because the kidney is anatomically and functionally immature. The neonate's capacity to conjugate drugs in the liver is often deficient. For example, the half-life of oxazepam (which is subject to glucuronidation) is three to four times longer in neonates than in adults.

Box 47.3 Measures to ensure the safety of the breastfed infant

Avoid unnecessary maternal drug use
Seek professional advice on the suitability of over-the-counter products
Avoid herbal products because of lack of data to support safe use
Assess the risk/benefit ratio for both mother and infant
Use the minimum clinically effective dose for the shortest possible time
Review maternal therapy towards the end of pregnancy
Choose a drug regimen and route of administration which presents the minimum of drug to the infant via breast milk
Avoid drugs known to cause serious toxicity in adults or children
Monitor the infant for unusual signs or symptoms
Avoid new drugs if there is a therapeutic equivalent with data to support safe use in lactation
Recognise risk factors, for example, prematurity, infant morbidity, multiple maternal medications

Table 47.6 Examples of commonly used drugs thought to be safe for use in breastfeeding mothers of full-term healthy infants[a]

Drug groups	Individual drugs
Antacids	Cetirizine
Bulk laxatives	Clotrimazole
Cephalosporins	Cromoglycate
Inhaled medications, for example, salbutamol	Diclofenac
Penicillins	Heparin
Progestogens	Ibuprofen
Vaccines (except smallpox)	Insulin
Vitamins (except high-dose A and D)	Iron supplements
	Lactulose
	Levothyroxine
	Loratadine
	Nystatin
	Paracetamol
	Warfarin

[a]This table is to be used as a guide only. Expert advice is required when the maternal dose is high, if the infant is premature, has renal or hepatic disease or G6PD deficiency.

Glucose-6-phosphate dehydrogenase deficiency

Infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency are susceptible to adverse effects even when only small amounts of certain drugs are present in milk. G6PD is an enzyme present in erythrocytes that is responsible for maintaining the antioxidant compound glutathione in its active form. Deficiency of this enzyme makes the erythrocyte more susceptible to oxidative stress, resulting in haemolysis. Only small amounts of drug are needed to cause such a reaction. Breastfeeding should be avoided or a safer alternative chosen if the infant has a known or suspected G6PD deficiency and the mother is taking drugs that have been reported to cause oxidative stress (e.g. nitrofurantoin, dapsone).

Allergy

The theoretical possibility exists for an allergic reaction in an infant exposed to a drug in breast milk. Even minimal exposure to the drug could cause an allergic response. However, in practice, such reactions are very rare and only if the infant has already experienced an allergic reaction to a particular drug should maternal use be discouraged or breastfeeding avoided.

Recreational drug use

Accurate details relating to maternal use of recreational drugs may be difficult to obtain. Usage may be chronic or sporadic. The role of the health professional in ensuring the safety of the breastfed infant is important, and the advice should be that substances such as cannabis, LSD and cocaine should be avoided whilst breastfeeding.

Significant amounts of alcohol pass into milk although it is not normally harmful to the infant if the quantity and duration of intake are limited. The occasional consumption of a small alcoholic beverage is acceptable if breastfeeding is avoided for about 2 h after the drink. Chronic or heavy consumers of alcohol should not breastfeed. High intakes of alcohol decrease milk let down and disrupt nursing until maternal levels decrease. Heavy maternal use may cause infant sedation, fluid retention and hormone imbalances in breastfed infants.

Nicotine has been suggested to decrease basal prolactin production although effects may be variable. Ideally, mothers should be encouraged not to smoke whilst breastfeeding. Nicotine and its metabolite, cotinine, are both present in milk. Undertaking smoking cessation with a nicotine patch is a safer option than continued smoking. Whilst transdermal nicotine patches produce a sustained lower nicotine plasma level, nicotine gums produce large variations in peak levels. A 2 -3 h washout period is recommended before breastfeeding after maternal use of a nicotine gum.

Caffeine appears in breast milk rapidly after maternal intake. Fussiness, jitteriness and poor sleep patterns have been reported in infants of mothers with very high caffeine intakes equivalent to about 10 or more cups of coffee daily. Preterm and newborn infants metabolise caffeine very slowly and are at increased risk of adverse effects.

Drug effects on lactation

Drugs that affect dopamine activity are the main cause of effects on milk production, mainly mediated by effects on prolactin. Early postpartum use of oestrogens may reduce the volume of milk, but the effect is variable and depends on the dose and the individual response. Progestogen contraceptives are preferred.

Drugs may occasionally be used therapeutically for their effect on lactation. Dopamine agonists such as cabergoline decrease milk production, and this effect may be utilised, for example, after an infant death. Dopamine agonists should not

be used routinely for relief of the symptoms of postpartum pain or engorgement which can be managed with simple analgesics or breast support. Dopamine antagonists such as domperidone may be used in cases of inadequate lactation which have not responded to first-line methods such as improved technique or milk expression by hand or pump.

Other drugs may affect lactation as an unwanted side effect, for example, diuretics. When these are used on a long-term basis, infant weight gain should be monitored.

Case studies

Case 47.1

A woman is 6 weeks' pregnant and has been diagnosed with depression that warrants pharmacological intervention. She wishes to recommence venlafaxine, which has been helpful in the past. She is also anxious that the ethanol she consumed around the time of conception may have harmed her baby.

Questions

1. What are the safest antidepressants in the first trimester of pregnancy?
2. Is it reasonable for her to commence venlafaxine?
3. Is there any risk from the ethanol ingestion?

Answers

1. Tricyclic antidepressants (TCAs) have been extensively used in pregnancy and are generally regarded as safe. For this reason, past practice was to recommend that TCAs should be used preferentially for the treatment of depression in pregnancy when considering teratogenic risk to the fetus. TCAs are, however, associated with side effects including risk of maternal cardiotoxicity, particularly in overdose. Further, available data on TCA use in pregnancy do not prove that they are less teratogenic than other antidepressant classes such as SNRIs and SSRIs. An antidepressant other than TCAs may therefore be appropriate for use in pregnancy, and the risks and benefits for each should be considered and ideally discussed with the patient on a case-by-case basis.
2. Experience with the use of venlafaxine and many other antidepressants, for example, moclobemide, in pregnancy is limited. However, in some instances, it may be necessary to use an agent such as venlafaxine. For example, if the mother had a history of severe depression that did not respond to multiple trials of other antidepressants, then venlafaxine may be considered the most appropriate choice of antidepressant for that woman. In this case, any potential risks associated with venlafaxine are likely to be less than those associated with inadequately treated depression.
3. Ethanol is a human teratogen. Fetal alcohol spectrum disorders are characterised by low birth weight, facial dysmorphogenesis and delayed development. A 'safe limit' for alcohol consumption in pregnancy has not been defined, and it is possible that very low amounts of alcohol may produce subtle effects on the fetus. Therefore, the best practice is to avoid all alcohol exposure in pregnancy. In this case, the mother ingested ethanol at the time of conception. She should be reassured that this is regarded as a relatively safe period and is not expected to adversely affect the fetus . However, further ethanol ingestion should be avoided.

Case 47.2

A 30-year-old woman with epilepsy is currently taking valproic acid 1500 mg daily. She wishes to conceive but is concerned about the possibility of birth defects due to valproate exposure in pregnancy. Her seizures have been difficult to control with alternative anticonvulsants.

Questions

1. What are the risks associated with valproate treatment in pregnancy?
2. How can these risks be minimised?

Answers

1. Valproate is a human teratogen, with early first-trimester exposure associated with a 1–2% risk of neural tube defects, as well as other malformations such as orofacial clefts. Valproate has also been associated with neonatal complications such as seizures. It is frequently advised that valproate is avoided in pregnancy and that the valproate dose should be gradually tapered and discontinued prior to conception. However, this is not a realistic option for many women with epilepsy. In fact, seizures may lead to greater problems such as maternal–fetal injury, miscarriage or hypoxia.
2. The patient should be reassured that most pregnancies in women with epilepsy end with a healthy baby without malformations. Concern about the risk of fetal abnormalities may result in reduced adherence, which may have greater maternal–fetal risk than the drug itself. As the patient is not yet pregnant, this is an optimal time for her current drug regime to be reviewed and optimised by a neurologist or health professional with expertise in managing women with epilepsy during pregnancy. There is some evidence to suggest that higher doses/concentrations of valproate are associated with greater risk of malformations. Where valproate remains the drug of choice, the lowest effective dose should be used throughout pregnancy. Monitoring free valproate concentrations may be useful in pregnancy, perhaps with the view to maintaining those concentrations shown to be effective in the non-pregnant stage. However, doses should be adjusted based on clinical need and not concentrations alone. Women with epilepsy should be commenced on high-dose folic acid 4–5 mg daily pre-conceptually. They should also be offered the option of prenatal diagnostic techniques that screen for neural tube defects such as ultrasound and serum α-fetoprotein.

Case 47.3

A 2-day-old full-term infant has excessive shrill crying, is jittery and is feeding poorly. The medical team cannot find any cause for these effects. The mother is worried that they may be due to paroxetine exposure via breast milk and wonders whether St John's wort would be a safer alternative. She has taken paroxetine 20 mg daily throughout pregnancy, and this has been continued after delivery.

You note from a specialist textbook that the likely infant exposure is about 2% of the weight-adjusted maternal dose.

Questions

1. What is the most likely drug-related explanation?
2. Is it safe for the mother to continue to take paroxetine whilst breastfeeding?
3. Is St John's wort a reasonable alternative?

Answers

1. The most likely explanation is a neonatal withdrawal syndrome from SSRI use near term. Symptoms typically occur 12 h–5 days after birth. The adult half-life of paroxetine is about 24 h, but this is much longer in a neonate. There will be a gradual decline in paroxetine plasma levels in the neonate after delivery. Drug exposure in pregnancy is much greater than exposure via milk. There may be some overlap of symptoms resulting from drug transfer into breast milk and from *in utero* exposure – agitation, jitteriness, hypotonia and gastro-intestinal symptoms. However, sedation has only been reported after drug exposure via breast milk. Paroxetine is one of the preferred SSRIs in breastfeeding as the half-life is shorter than most members of the group and the incidence of reported adverse effects is low.
2. The mother should be reassured that the effects are not due to the transfer of excessive amounts of paroxetine into milk. Withdrawal symptoms usually settle after a few days, whereas adverse effects due to the drug via milk will remain with continued exposure. If symptoms persist, further medical advice should be sought.
3. Herbal remedies are often perceived as safe as they are natural. In general, there is a lack of data to support the safe use of herbal remedies in lactation, and their use should be avoided. If a pharmacological treatment is indicated, then a drug for which data in lactation is available, for example, paroxetine should be used.

Case 47.4

A breastfeeding mother returned to see her midwife 4 weeks after delivery of a full-term healthy infant. She is complaining of bilateral nipple pain during and after breastfeeding, a problem that was constant for the past 4 days. She was advised to use miconazole cream 2% to the nipples after each feed. This provided initial relief but symptoms returned after a few days. She was given a course of fluconazole 200 mg daily for 14 days for a presumed candidal infection but expressed concern that the medication might affect the infant.

Questions

1. Is this regimen safe to use in lactation?
2. What other therapeutic measures should be taken?

Answers

1. Topical miconazole is effective in treating superficial candidal infections, but oral therapy with fluconazole is needed when the infection spreads to the milk ducts. Assuming a mean fluconazole milk level of 2.3 mg/L, an infant weight of 4 kg and a milk intake of 150 mL/kg/day:

   The estimated daily infant intake via milk will be 2.3 × 0.15 × 4 = 1.38 mg or 0.345 mg/kg/day.

   This represents 10.35% of the weight-adjusted dose for a 60-kg woman taking 200 mg of fluconazole daily and 5.75% of the paediatric dose of 6 mg/kg/day. The mother may be reassured that the amount of drug reaching the infant via milk is only a small fraction of the dose that would be used to treat an infection in the infant.
2. Candidal infections are easily passed between the mother and the infant, and both should receive treatment. Infants can be treated with nystatin suspension or oral miconazole gel. The latter is not suitable for young infants under 4 months because of the risk of choking on the viscous formulation, and care is still needed with older infants.

Case 47.5

A mother who wishes to give up smoking seeks advice on the safety of nicotine replacement therapy (NRT) whilst breastfeeding. She is currently in the latter stages of pregnancy but does not wish to use these products until after delivery and has not been successful in significantly reducing her smoking without aids.

Questions

1. What effect is smoking likely to have on breastfeeding?
2. Can NRT be used safely whilst breastfeeding?
3. If so, which products are preferred?

Answers

1. Women who smoke during pregnancy are less likely to breastfeed and more likely to wean their infants earlier. Nicotine reduces basal prolactin levels which may lead to a decrease in milk supply. It also causes adrenaline release which may inhibit the release of oxytocin and affect the milk let-down reflex. Tobacco smoke may produce breathing difficulties and other problems in infants. Maternal smoking is a major factor for sudden infant death syndrome (SIDS) and breastfeeding provides significant protection.
2. Ideally, breastfeeding mothers should stop smoking, preferably by using non-pharmacological methods. If this is not possible, most authorities advise that the amount of nicotine passing into milk after use of NRT is very much smaller than that after smoking and less harmful than the second-hand smoke an infant might breathe if the mother continues to smoke. NRT products are devoid of tars, carbon monoxide and respiratory irritants found in cigarettes. Where the infant has breathing difficulties, NRT should be avoided. Other members of the household who smoke should also be encouraged to give up smoking.
3. Breast milk levels of nicotine after use of a 21-mg transdermal patch are roughly equivalent to smoking 17 cigarettes a day. Maternal plasma levels of nicotine after using a nicotine spray are about one-third those of smokers and levels after using a gum are variable but can be similar to those seen after smoking. If possible, nicotine patches should be avoided during breastfeeding because they provide a continuous (but low) passage of nicotine into breast milk. If patches are used, they should be removed at night time to decrease nocturnal exposure. For shorter-acting preparations (e.g. gums, lozenges), it is best to breastfeed immediately before use and allow a 2–3 hour period before resumption of breastfeeding to minimise infant exposure.

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Useful websites

UK Teratology Information Service (UKTIS):
www.uktis.org

TOXBASE:
www.toxbase.org

European Network of Teratology Information Services:
http://www.entis-org.com

OTIS (American Organisation of Teratology Information Services):
www.otispregnancy.org

Motherisk (Canadian Teratology information service):
www.motherisk.org.