12 Peptic ulcer disease

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Key points

- The two main types of peptic ulcer disease are those associated with *Helicobacter pylori* and those associated with non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin.
- Ulcer-like dyspepsia does not correlate with diagnosis of peptic ulcer.
- Uninvestigated dyspepsia without alarm symptoms may be treated empirically without an endoscopic diagnosis.
- An *H. pylori* test and treat strategy means it is unknown if the patient has an ulcer.
- Triple therapy with a proton pump inhibitor (PPI), clarithromycin and amoxicillin twice daily for 7 days is currently the recommended first-line *H. pylori* eradication regimen.
- Patient adherence influences the success of *H. pylori* eradication therapy.
- *H. pylori* eradication therapy does not have a role in the management of gastro-oesophageal reflux disease (GORD). Its benefit in the management of functional dyspepsia is small.
- Associated risks of *Clostridium difficile* infection, pneumonia and osteoporosis have led to judicious use of PPIs.
- Patients who need to continue NSAID therapy are the only patients with peptic ulcer disease in whom continued ulcer-healing therapy is necessary after the ulcer has healed and *H. pylori* has been eradicated.
- Upper gastro-intestinal symptoms in NSAID users do not correlate well with presence or absence of peptic ulcers.
- The risk of ulcers associated with NSAID use is common to all non-specific NSAIDs and is dose dependent. The risk is maintained during treatment and decreases once treatment is stopped.
- Risk factors for NSAID-induced gastro-intestinal complications include previous history of peptic ulcer or gastro-intestinal bleeding, age >65, concomitant use of aspirin, anticoagulants or corticosteroids.
- Adding a PPI to non-specific NSAIDs provides a similar reduction in risk of gastro-intestinal toxicity to that offered by cyclo-oxygenase-2 (COX-2) inhibitors alone.
- Enteric coating or taking them with food does not reduce the risk of upper gastro-intestinal bleeding associated with NSAIDs and low-dose aspirin.
- Adding a PPI to aspirin is associated with lower risk of recurrent gastro-intestinal bleeding than clopidogrel alone.
- Concomitant PPI therapy may decrease clopidogrel activity through competitive hepatic metabolism; the combination is not recommended unless dual antiplatelet therapy is indicated.
- *H. pylori* eradication has a greater effect on decreasing recurrent peptic ulcer bleeding rate than PPIs alone in patients who continue low-dose aspirin; an additive effect is seen if both strategies are used.
- Cardiovascular risks must be weighed against gastro-intestinal risks in deciding whether or not to discontinue aspirin and for how long in patients who present with gastro-intestinal bleeding.
- Approximately one-third of deaths from gastro-intestinal bleeding are due to NSAIDs, and up to one-third of NSAID/aspirin deaths are attributed to low-dose aspirin.
- High dose intravenous PPI therapy is indicated to prevent re-bleeding in patients at high risk (active bleeding or non-bleeding visible vessel) following endoscopic haemostatic treatment for bleeding peptic ulcer. It is not recommended in those at low risk or pre-endoscopy.
- *H. pylori* eradication reduces re-bleeding rate in patients with gastro-intestinal bleeding but eradication treatment can be delayed until normal oral intake is resumed.
- Adding a PPI to a COX-2 inhibitor (in those not at cardiovascular risk) decreases the re-bleeding rate in those patients at high risk of re-bleeding in comparison to COX-2 inhibitors alone. No comparison has been made with non-selective NSAID in combination with PPI.

The term ‘peptic ulcer’ describes a condition in which there is a discontinuity in the entire thickness of the gastric or duodenal mucosa that persists as a result of acid and pepsin in the gastric juice (Fig. 12.1). Oesophageal ulceration due to acid reflux is generally classified under GORD. This definition excludes carcinoma and lymphoma, which may also cause gastric ulceration, and also excludes other rare causes of gastric and duodenal ulceration such as Crohn's disease, viral infections and amyloidosis. About 10% of the population in developed countries is likely to be affected at some time by peptic ulcer, with the prevalence for active ulcer disease being about 1% at any particular point in time.

Peptic ulcer disease often presents to clinicians as dyspepsia. However, not all patients with dyspepsia have peptic ulcer disease. Dyspepsia is defined as persistent or recurrent pain or discomfort centred in the upper abdomen. The most common causes of dyspepsia are non-ulcer or functional dyspepsia, GORD and peptic ulcer. Other causes include gastric cancer, pancreatic or biliary disease. Peptic ulcer accounts for 10–15% of dyspepsia, and oesophagitis for about 20%. However, 60–70% of patients have no obvious abnormality and have functional dyspepsia or endoscopy-negative GORD. Dyspepsia is a common symptom and affects about 40% of

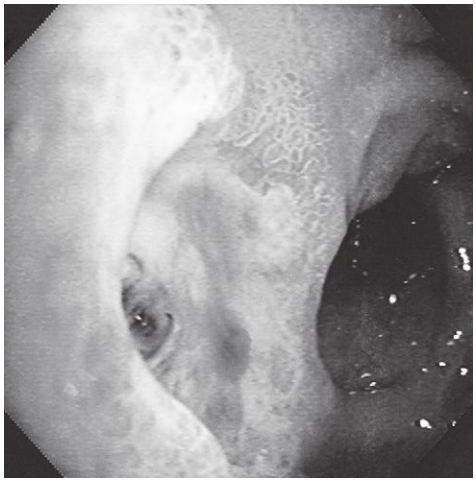


Fig. 12.1 Duodenal ulcer seen at endoscopy. Note also a visible blood vessel that is a stigma of recent haemorrhage.

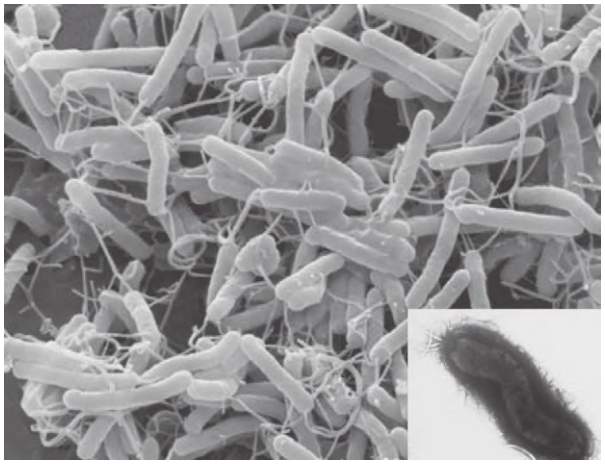


Fig. 12.2 *Helicobacter pylori*. The Gram-negative spiral bacterium *H. pylori*, formerly known as *Campylobacter pylori*, was isolated serendipitously from patients with gastritis by Barry Marshall and Robin Warren in 1982. Seven years later, it was conceded that *H. pylori* is responsible for most cases of gastric and duodenal ulcer.

people annually. It is the reason for 5–10% of consultations with primary care physicians, and up to 70% of referrals to gastro-intestinal units are patients with dyspepsia. However, the widely adopted test and treat recommendation for uninvestigated dyspepsia has reduced endoscopy referrals.

Epidemiology

The incidence of duodenal ulcer is now declining, which follows the decline in *H. pylori* infection. However, hospital admission rates for gastro-intestinal bleeding associated with gastric and duodenal ulcers are rising, especially in older patients. This is probably a consequence of increased prescriptions for low-dose aspirin, NSAIDs, antiplatelets, anticoagulants and selective serotonin reuptake inhibitors (SSRI). Over the previous decade there has been an increase in idiopathic peptic ulcer disease in patients who test negative for *H. pylori* and who do not take NSAIDs or aspirin. In some countries, up to one-quarter of peptic ulcers are idiopathic and there is a decrease in prevalence of *H. pylori* infection. Idiopathic ulcers should be investigated to attempt to identify the underlying cause following careful reassessment of *H. pylori* status and medication history.

Infection by *H. pylori*, a spiral bacterium of the stomach, remains an important epidemiological factor in causing peptic ulcer (Fig. 12.2). Most *H. pylori* infections are acquired by oral–oral and oral–faecal transmission. The most important risk factors for *H. pylori* infection are low social class, overcrowding and home environment during childhood, for example, bed sharing. Transmission may occur within a family, a fact demonstrated by the finding that family members, especially spouses, may have the same strain of *H. pylori*. *H. pylori* seropositivity increases with age as colonisation persists for the lifetime of the host. Subjects who become infected with *H. pylori* when young are more likely to develop chronic or atrophic gastritis with reduced acid secretion that may protect them from developing duodenal ulcer. However, it may promote development of gastric ulcer as well as gastric cancer. Duodenal ulcer seems to develop in those who are infected with *H. pylori* at the end of childhood or later. Historically, developing countries have a higher ratio of duodenal ulcer to gastric ulcer but as rates of *H. pylori* infection decline with improvements in hygiene and rates of gastric ulcer increase with the use of ulcerogenic drugs, this ratio of duodenal to gastric ulcer is declining. The prevalence of *H. pylori* still tends to be higher in the Asian adult population in whom a lower parietal cell mass has been found. These factors together with slower metabolism may explain the greater efficacy of PPIs in Asian populations. There may be other genetic, environmental or cultural factors influencing peptic ulcer disease.

Pathogenesis

There are two common forms of peptic ulcer disease: those associated with the organism *H. pylori* and those associated with the use of aspirin and NSAIDs. Less common is ulcer disease associated with massive hypersecretion of acid which occurs in the rare gastrinoma (Zollinger–Ellison) syndrome.

Helicobacter pylori

This organism is a Gram-negative microaerophilic bacterium found primarily in the gastric antrum of the human stomach (see Fig. 12.2). Ninety-five percent or more of duodenal ulcers and 80–85% of gastric ulcers are associated with *H. pylori*. The bacterium is located in the antrum and the acid-secreting microenvironment of the corpus of the stomach is less hospitable to the bacterium. In the developed world, reinfection rates are low, about 0.3–1.0% per year, whereas in the developing world reinfection rates are higher, approximately 20–30%. Ulcerogenic strains of *H. pylori*, ulcer-prone hosts, age of infection and interaction with other ulcerogenic factors such as NSAIDs determine peptic ulcer development

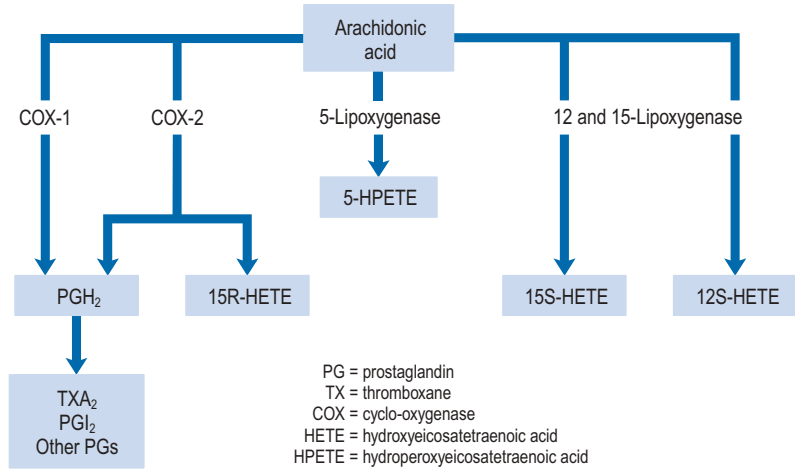


Fig. 12.3 Arachidonic acid pathway.

following *H. pylori* infection. The contribution of *H. pylori* infection to the risk of ulcers in NSAID users is not clear but there appears to be an additive effect. The risk of peptic ulcer in long-term NSAID users is greater in those who test positive for *H. pylori* and eradication of *H. pylori* in these patients prior to commencing NSAID treatment has been shown to reduce the risk of *H. pylori* NSAID-associated peptic ulcer.

Although the majority of species in the *H. pylori* genus have been associated with pathology, some are more virulent than others which probably explains why, in combination with host-related factors, only 5–10% of those infected go on to develop peptic ulcer disease.

The underlying pathophysiology associated with *H. pylori* infection involves the production of cytotoxin-associated gene A (*CagA*) proteins and vacuolating cytotoxins, such as vac A, which activate the inflammatory cascade. *CagA* status and one genotype of the vac A gene are also predictors of ulcerogenic capacity of a strain. In addition, a number of enzymes produced by *H. pylori* may be involved in causing tissue damage and include urease, haemolysins, neuraminidase and fucosidase.

Gastrin is the main hormone involved in stimulating gastric acid secretion, and gastrin homeostasis is also altered in *H. pylori* infection. The hyperacidity in duodenal ulcer may result from *H. pylori*-induced hypergastrinaemia. The elevation of gastrin may be a consequence of bacterially mediated decrease of antral D cells that secrete somatostatin, thus losing the inhibitory modulation of somatostatin on gastrin, or direct stimulation of gastrin cells by cytokines liberated during the inflammatory process. Long-standing hypergastrinaemia leads to an increased parietal cell mass. High acid content in the proximal duodenum leads to metaplastic gastric-type mucosa, which provides a niche for *H. pylori* infection followed by inflammation and ulcer formation.

Non-steroidal anti-inflammatory drugs

Three patterns of mucosal damage are caused by NSAIDs. These include superficial erosions and haemorrhages, silent ulcers detected at endoscopy and ulcers causing clinical symptoms and complications. Weak acid NSAIDs, such as acetylsalicylic acid, are concentrated from the acidic gastric juice into mucosal cells, and may produce acute superficial erosions via inhibition of COX and by mediating the adherence of leucocytes to mucosal endothelial cells. Enteric coating may prevent this superficial damage but does not demonstrate any clinical benefit in terms of reduction of gastro-intestinal bleeding or ulceration (Bhatt et al., 2008). The major systemic action of NSAIDs that contributes to the formation of ulcers is the reduction of mucosal prostaglandin production. All NSAIDs share the ability to inhibit COX (Fig. 12.3). The presence of NSAID-induced ulcers does not correlate with abdominal pain and NSAIDs themselves often mask ulcer pain. Approximately 20% of patients taking NSAIDs experience symptoms of dyspepsia but symptoms correlate poorly with the presence of mucosal damage. Ulcers and ulcer complications occur in approximately 4% of NSAID users every year. Patients taking NSAIDs have a four-fold increase in risk of ulcer complications compared with non-users. The risk of ulcer bleeding in low-dose aspirin users is two- to three-fold and there may be differences in risk factors. For example, the risk with aspirin is less influenced by age than the risk associated with NSAIDs (McQuaid and Laine, 2006) and *H. pylori* may have greater influence on the risk of bleeding with low-dose aspirin than with NSAIDs (Lanza et al., 2009).

Each year, in the UK population over the age of 60 years, there are ~3500 hospitalisations and over 400 deaths associated with NSAIDs. The risk of ulcer complications (Box 12.1) is progressive depending upon the number of risk factors present (Lanza et al., 2009). The most important risk factors

Box 12.1 Risk factors for NSAID ulcers

Age greater than 65 years
Previous peptic ulceration/bleeding
High dose of NSAID or more than one NSAID (including aspirin)
Short-term history of NSAID use (<1 month)
Concomitant corticosteroid or anticoagulant use
Cardiovascular disease

are a history of ulcer complications and advancing age, particularly over 75 years. Ulcers have been found to be more common in patients who have taken NSAIDs for less than 3 months, with the highest risk observed during the first month of treatment. The risk increases with higher doses of NSAID but mucosal damage occurs with even very low doses of NSAIDs, particularly aspirin. Corticosteroids alone are an insignificant ulcer risk, but potentiate the ulcer risk when added to NSAIDs, particularly in daily doses of at least 10 mg prednisolone (Lanza et al., 2009).

Low-dose aspirin (75 mg/day) alone increases the risk of ulcer bleeding and this effect may be due to the antiplatelet action, independent of other risk factors. Concomitant use of aspirin with NSAIDs further increases the risk. There is no evidence that anticoagulants increase the risk of NSAID ulcers but they are associated with an increase in the risk of haemorrhage. The presence of cardiovascular disease is also considered as an independent risk factor.

Selective cyclo-oxygenase-2 inhibitors

The gastro-intestinal side effects of conventional NSAIDs are mediated through the inhibition of COX-1 (see Fig. 12.3). COX-1 stimulates synthesis of homeostatic prostaglandins while COX-2 is predominantly induced in response to inflammation. Selective COX-2 inhibitors tend not to reduce the mucosal production of protective prostaglandins to the same extent as NSAIDs. COX-2 inhibitors are, therefore, considered to be safer than non-selective NSAIDs in patients at high risk of developing gastro-intestinal mucosal damage. Although studies have confirmed the reduction of endoscopic and symptomatic ulcers (Hooper et al., 2004), an increase in cardiovascular risk, including heart attack and stroke, has resulted in the withdrawal of some COX-2 inhibitors from the market. Additional contraindications are now in place for those COX-2 inhibitors that remain on the market. Amongst the new contraindications is the recommendation that they should not be taken by patients with established heart or cerebrovascular disease, or taken in combination with low-dose aspirin as this negates any beneficial gastro-intestinal protective effects. The need for and choice of anti-inflammatory agent should therefore take into account gastro-intestinal, cardiovascular and other risks such as potential cardio-renal effects. For all agents, the lowest effective dose should be used for the shortest duration.

Candidates for COX-2 inhibitors are patients at high risk of NSAID-related gastro-intestinal events but who do not require low-dose aspirin therapy. The lowering of risk of gastro-intestinal events is similar for COX-2 inhibitors and non-selective NSAIDs combined with a gastroprotective agent.

Nitric oxide-releasing NSAIDs

Nitric oxide (NO)-releasing NSAIDs are being investigated to see if the gastric mucosa protection associated with nitric oxide prevents ulceration when prostaglandins are inhibited by NSAIDs (Fiorucci et al., 2007). Nitric oxide is coupled to the NSAID via an ester, resulting in prolonged release of nitric oxide. Nitric oxide itself has anti-inflammatory effects adding to the potency of the NSAID. Animal studies suggest NO-releasing agents, such as naproxcinod, have minimum cardiovascular and gastro-intestinal toxicity.

Clinical manifestations

Upper abdominal pain occurring 1–3 h after meals and relieved by food or antacids is the classic symptom of peptic ulcer disease. The relationship to meals is more marked in duodenal ulcer than in gastric ulcer. However, the symptoms of peptic ulcer disease lack specificity; they do not distinguish between duodenal ulcer, gastric ulcer or functional dyspepsia. Anorexia, weight loss, nausea and vomiting, heartburn and eructation can all occur with peptic ulcer disease. Patients with predominant symptoms of heartburn are likely to have GORD. Complications of peptic ulcer disease may occur with or without previous dyspeptic symptoms. These are haemorrhage, chronic iron-deficiency anaemia, pyloric stenosis and perforation. In the elderly, the presentation is more likely to be silent and gastro-intestinal bleeding may be the first clinical sign of disease. Peptic ulcer bleeding is the most frequent and severe complication of peptic ulcer disease. Physical examination may be negative or reveal epigastric tenderness. Peptic ulcers in the past tended to relapse and remit, and 70–80% of ulcers relapse within 1–2 years after being healed by antisecretory therapy. This tendency to relapse is dramatically reduced by eradication of *H. pylori*.

Patient assessment

Presenting symptoms of dyspepsia require careful assessment to judge the risk of serious disease or to provide appropriate symptomatic treatment. Symptom subgroups such as ulcer, reflux and dysmotility type may be useful in identifying the predominant symptom subgroup to which a patient belongs. Many patients have symptoms which fit more than one subgroup (Box 12.2). Many patients seek reassurance, lifestyle advice and symptomatic treatment with a single consultation, others have chronic symptoms. In some cases, medications may be the cause of dyspepsia and should be reviewed (Box 12.3).

Patients at any age who present with alarm features (Box 12.4) should be referred for endoscopic investigation. These groups of patients are at a higher risk of underlying serious disease such as cancer, ulcers or severe oesophagitis. Referral is also recommended for patients over the age of 55 if symptoms are unexplained or persistent despite initial management (NICE, 2004; SIGN, 2003). Malignant disease is rare in young people and in those without alarm features.

Patients with predominant reflux-like symptoms are likely to respond to acid-suppressing therapy and one month's treatment of standard dose of PPI should be given in patients whose symptoms persist despite antacid and lifestyle adjustment. Eradication of *H. pylori* is not beneficial in GORD.

Box 12.2 Dyspepsia symptom subgroups

Reflux-like dyspepsia
Heartburn plus dyspepsia
Acid regurgitation plus dyspepsia
Ulcer-like dyspepsia
Localised epigastric pain
Pain when hungry
Pain relieved by food
Pain relieved by antacids or acid-reducing drugs
Pain that wakens the patient from sleep
Pain with remission and relapses
Dysmotility-like dyspepsia
Upper abdominal discomfort (pain not dominant)
Early satiety
Postprandial fullness
Nausea
Retching or vomiting
Bloating in the upper abdomen (no visible distension)
Upper abdominal discomfort often aggravated by food
Unspecified dyspepsia

Box 12.3 Drugs causing dyspepsia

Antibiotics
Bisphosphonates
Calcium channel blockers
Corticosteroids
Drugs with antimuscarinic effects, for example, tricyclic antidepressants
Iron
Nitrates
NSAIDs including aspirin
Potassium chloride
Theophylline

Box 12.4 Alarm features

Dysphagia
Pain on swallowing
Unintentional weight loss
Gastro-intestinal bleeding or anaemia
Persistent vomiting
On NSAIDs or warfarin

In those patients who do not have reflux-like dyspepsia, testing for the presence of *H. pylori* is recommended. Eradication treatment should be prescribed for those who test positive and empirical acid suppression for those who test negative. The small proportion of patients with symptoms due to ulcers should be cured. Overall, in functional dyspepsia, symptom control is poor but a small and significant benefit of eradication treatment has been shown. Acid suppression is only of benefit in a small proportion of patients with functional dyspepsia. There is no evidence to support other pharmacological therapies and non-pharmacological strategies may have a future role in functional dyspepsia. Patients should be reassured that the condition is common and not serious. National guidelines (NICE, 2004) provide algorithms to guide practitioners through the management of patients presenting with dyspepsia (Fig. 12.4A and B).

Investigations

Endoscopy

Endoscopy is generally the investigation of choice for diagnosing peptic ulcer, and the procedure is sensitive, specific and safe. However, it is also invasive and expensive. Routine endoscopy in patients presenting with dyspepsia without alarm features (see Box 12.4) is not necessary. Endoscopic investigation should be undertaken in patients with alarm features and in those patients over 55 years who present with unexplained or persistent symptoms of dyspepsia. Biopsies may be taken to exclude malignancy and uncommon lesions such as Crohn's disease.

Patients with upper gastro-intestinal bleeding have traditionally undergone endoscopy whether as an emergency or on the next available list. Most patients do not require endoscopy and in those at low risk, endoscopy and admission to hospital can be avoided by application of a scoring system. The most widely used is the Rockall risk scoring system which includes endoscopic findings to predict poor outcome. Pre-endoscopic scoring systems are available (Stanley et al., 2009) such as the abbreviated Rockall score or the Glasgow–Blatchford score (GBS) which identify low-risk patients who can be managed safely without endoscopy or admission to hospital.

Wireless capsule endoscopy is also available to investigate NSAID-induced ulceration of the small intestine causing gastro-intestinal haemorrhage and is preferable to radiological imaging.

Radiology

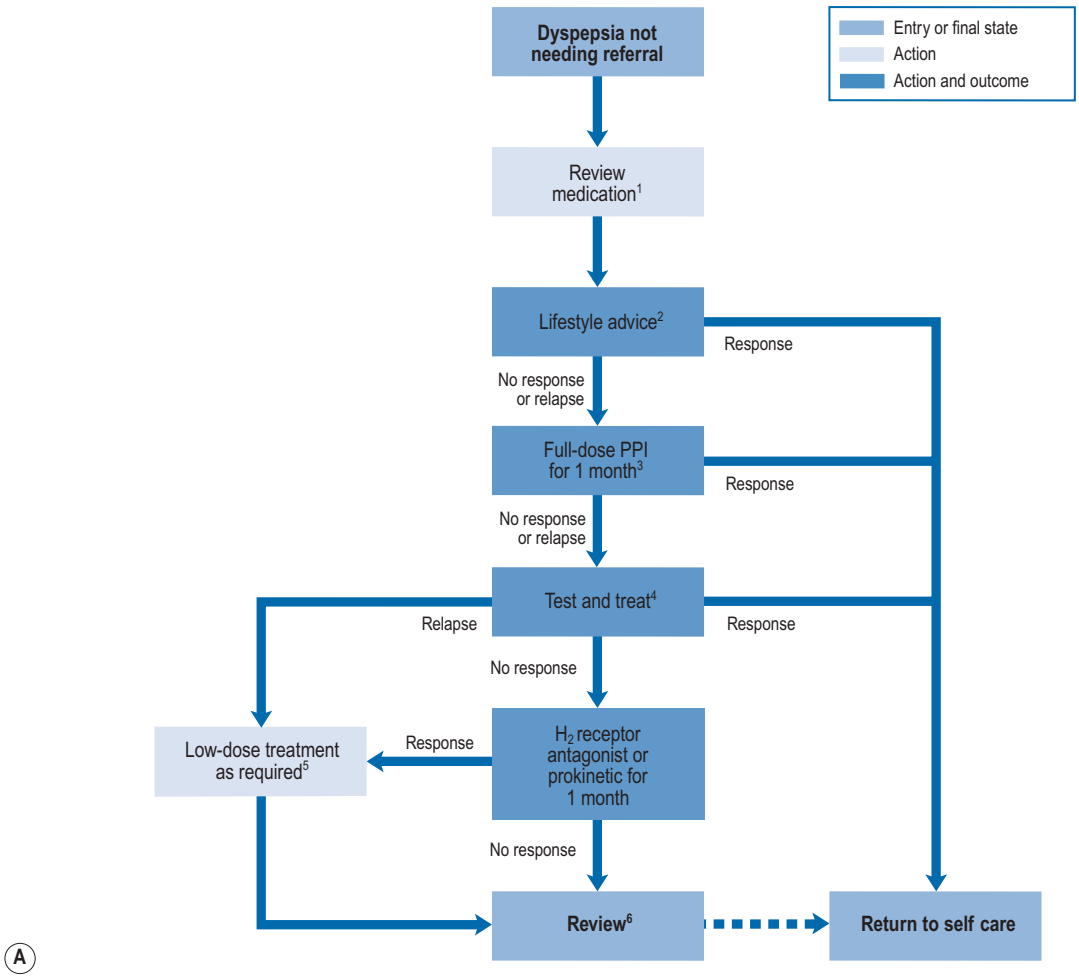
Double-contrast barium radiography should detect 80% of peptic ulcers. However, endoscopy is more accurate and almost always preferred. A Gastrografin® meal is used to diagnose peptic perforation in patients presenting with an acute abdomen, if a plain abdominal X-ray is not diagnostic.

H. pylori detection

There are several methods of detecting *H. pylori* infection. They include non-invasive tests such as serological tests to detect antibodies, [^{13}C] urea breath tests and stool antigen tests. Urea breath tests have a sensitivity and specificity over 90% and are accurate for both initial diagnosis and confirmation of eradication. The breath test is based on the principle that urease activity in the stomach of infected individuals hydrolyses urea to form ammonia and carbon dioxide. The test contains carbon-labelled urea which, when hydrolysed, results in production of labelled carbon dioxide which appears in the patient's breath. The stool antigen test uses an enzyme immunoassay to detect *H. pylori* antigen in stool. This test also has a sensitivity and specificity over 90% and can be used in the initial diagnosis and also to confirm eradication. However, the

breath test is preferable and more convenient. Serological tests are based on the detection of anti-*H. pylori* IgG antibodies but are not able to distinguish between active or previous exposure to infection. Near patient serology tests are not recommended (Malfertheiner et al., 2007) as they are inaccurate.

Invasive tests requiring gastric antral biopsies include urease tests, histology and culture. Of these, the biopsy urease test is widely used. Agar-based biopsy urease tests are designed to be read at 24 h, whereas the strip-based biopsy urease tests can be read at 2 h following incubation with the biopsy material.



1 Review medications for possible causes of dyspepsia, for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids and NSAIDs.

2 Offer lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation, promoting continued use of antacid/alginates.

3 There is currently inadequate evidence to guide whether full dose PPI (proton pump inhibitor) for 1 month or *H. pylori* test and treat should be offered first. Either treatment may be tried first with the other offered if symptoms persist or return.

4 Detection: use carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory based serology.
Eradication: use PPI, amoxicillin, clarithromycin 500 mg (PAC_{500}) regimen or a PPI, metronidazole, clarithromycin 250 mg (PAC_{250}) regimen.
Do not retest even if dyspepsia remains unless there is a strong clinical need.

5 Offer low-dose treatment with a limited number of repeat prescriptions. Discuss the use of treatment on an as-required basis to help patients manage their own symptoms.

6 In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist for a second opinion. Emphasise the benign nature of dyspepsia. Review long-term patient care at least annually to discuss medication and symptoms.

Fig. 12.4 (A) Decision algorithm for management of uninvestigated dyspepsia.

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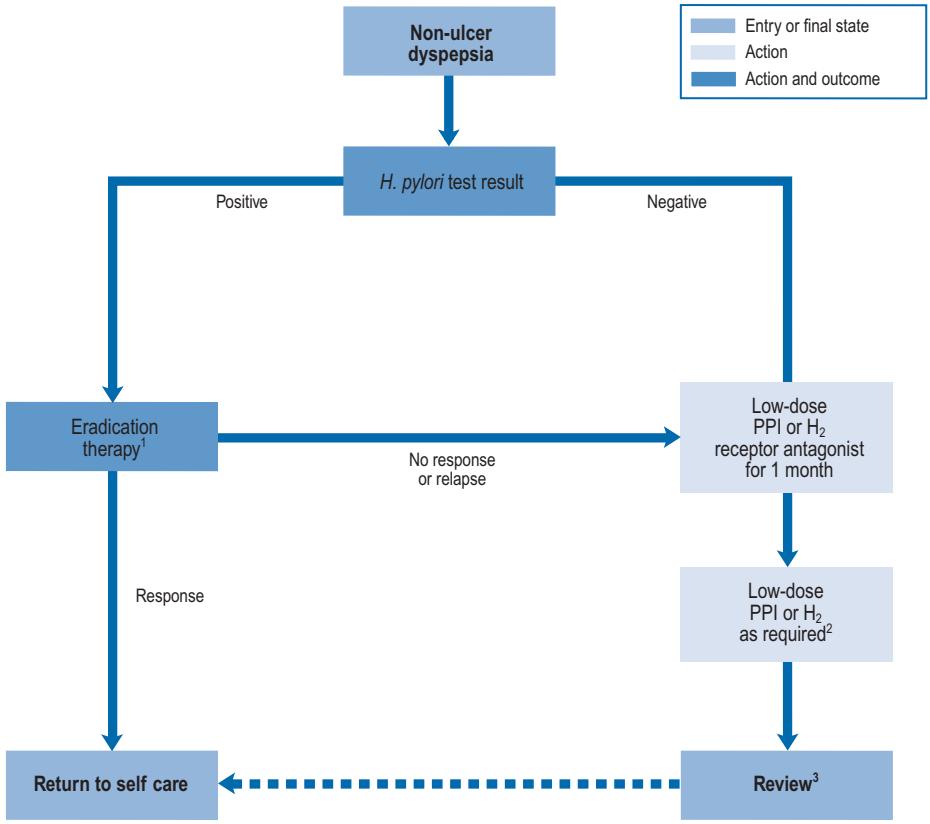


(B)

1 Use a proton pump inhibitor (PPI), amoxicillin, clarithromycin 500 mg (PAC_{500}) regimen or a PPI, metronidazole, clarithromycin 250 mg (PAC_{250}) regimen. Do not retest unless there is a strong clinical need.

2 Offer low-dose treatment, possibly on an as-required basis, with a limited number of repeat prescriptions.

3 In some patients with an inadequate response to therapy or new emergent symptoms it may become appropriate to refer to a specialist for a second option. Emphasise the benign nature of dyspepsia. Review long-term patient care at least annually to discuss medication and symptoms.

Fig. 12.4, cont'd (B) Decision algorithm for management of non-ulcer dyspepsia.

Increasing the number of biopsy samples increases the sensitivity of the test as infection can be patchy. The accuracy of the urea breath test or biopsy urease test can be reduced by drug therapy; therefore, it is recommended to discontinue PPIs at least 2 weeks before testing and discontinue antibiotics at least 4 weeks before testing to reduce the risk of false-negative results.

The faecal occult blood test is not specific for or sensitive to detection of NSAID-induced gastric damage. A full blood count may provide evidence of blood loss from peptic ulcer.

Treatment

Complications of peptic ulcer disease

Bleeding peptic ulcer

Peptic ulcer is the most common cause of non-variceal upper gastro-intestinal bleeding. Most patients with bleeding peptic ulcer are clinically stable and stop bleeding without any intervention, whereas other outcomes include re-bleeding and mortality. Endoscopy allows identification of the severity of disease as well as endoscopic haemostatic therapy which is successful in reducing mortality. Endoscopic therapy is necessary only in patients who exhibit high-risk stigmata (active bleeding, non-bleeding visible vessel, adherent clot) on endoscopy.

A number of pharmacological agents have been used for endoscopic injection therapy such as 1:10,000 adrenaline (epinephrine), human thrombin and fibrin glue. Mechanical endoscopic treatment options include thermocoagulation using a heater probe or endoscopic clipping. Combination therapies are superior to monotherapy and a combination of adrenaline 1:10,000 with either thermal or mechanical treatment is recommended (SIGN, 2008; Barkun et al., 2010). Need for surgery, re-bleeding rates and mortality are reduced but bleeding recurs in about 10% of patients and can cause death. Patients with uncontrolled bleeding should receive repeat endoscopic treatment, arterial embolisation

or surgery. The risk of recurrent bleeding following endoscopic therapy is reduced by increasing intragastric pH during the first 3 days after the initial bleed and eradication of *H. pylori*. Biopsies taken at the time of endoscopy are used to detect *H. pylori*, or the urea breath test can be used once oral intake is established and *H. pylori* eradication therapy is indicated in those who test positive. Successful eradication of *H. pylori* reduces the rate of re-bleeding to a greater extent than antisecretory non-eradicating therapy (Gisbert et al., 2004). Following successful *H. pylori* eradication and healing of the ulcer, there is no need to continue maintenance antisecretory therapy beyond 4 weeks unless required for prophylaxis of ulcer complications in those continuing to take aspirin or NSAIDs (SIGN, 2008).

Acid suppression reduces the re-bleeding rate and should be given to those patients at high risk of re-bleeding following endoscopic haemostatic therapy. The rationale for this is based on the fact that gastric acid inhibits clot formation and if intragastric pH is maintained above 6 during the first 3 days after the initial bleed, there is opportunity for clot stabilisation and haemostasis. Meta-analysis suggests PPIs significantly reduce re-bleeding rates compared with H_2-receptor antagonists and are the preferred choice of treatment (Leontiadis et al., 2006). In similar dosage regimens, there is no data to suggest any PPI is more efficacious than another. The optimal dose and route of PPI is unknown in this indication, although reduction in mortality is observed in high-risk patients when high dose PPI therapy is given (e.g. 80 mg bolus omeprazole, pantoprazole or esomeprazole followed by 8 mg/h for 72 h) following endoscopic haemostasis (Leontiadis et al., 2007; SIGN, 2008; Barkun et al., 2010).

The use of intravenous PPI therapy before endoscopy in patients with upper gastro-intestinal bleeding does not affect clinical outcome such as re-bleeding, need for surgery or mortality (Dorward et al., 2006). However, this may reduce the need for endoscopic therapy (Lau et al., 2007) as demonstrated in Asian patients in whom PPIs are more effective. Its benefits are not clear and it is not possible to identify patients with a greater likelihood of being at high risk. Therefore, the use of PPIs is not recommended prior to diagnosis by endoscopy (SIGN, 2008) but may be beneficial if early endoscopy is delayed (Barkun et al., 2010).

In those patients at low risk for re-bleeding and in whom endoscopic therapy is not indicated, usual therapeutic doses of oral PPI are given for 4 weeks to heal the ulcer. Aspirin or NSAIDs should be avoided but if strongly indicated, these patients are given concomitant PPI therapy following successful eradication of *H. pylori*. The effect of *H. pylori* eradication on the risk of recurrent ulcer bleeding is greater in patients taking low-dose aspirin than in those taking NSAIDs (Chan et al., 2001). A possible explanation (Lanza et al., 2009) for this might be that aspirin provokes bleeding in *H. pylori* ulcers and after healing, aspirin is less likely to cause ulceration.

In patients for whom there is a clear indication to continue aspirin therapy, addition of a PPI is of benefit in the prevention of recurrent bleeding in aspirin users (Lai et al., 2002). Clopidogrel alone is not a safer alternative than this combination in terms of prevention of recurrent ulcer bleeding. Cardiovascular and gastro-intestinal risks must be taken into consideration when deciding how long aspirin should be discontinued after a gastro-intestinal bleed. In some cases, low-dose aspirin can be restarted with concurrent PPI treatment within 7 days (Barkun et al., 2010). When the combination of aspirin and clopidogrel is indicated, concomitant PPI therapy is recommended in patients at high risk of gastro-intestinal complications despite the potential drug interaction between PPIs and clopidogrel. An increased risk of myocardial infarction has been observed with the combination of clopidogrel and PPIs (MHRA, 2009). Causality is unclear but it is suggested that through competitive enzyme inhibition, PPIs metabolised by CYP2C19 reduce the conversion of clopidogrel to its active metabolite. Concomitant use is discouraged but if necessary, separation of dosage timing is recommended (Laine and Hennekens, 2010).

Pyloric stenosis

Malignancy is the most common cause of gastric outlet obstruction. Peptic ulcer disease is the underlying cause in about 10% of cases. There is limited anecdotal evidence that incomplete gastric outlet obstruction may improve within several months of successful *H. pylori* eradication. Conventional treatment with acid-suppressive therapy may also help. If medical therapy fails to relieve the obstruction, endoscopic balloon dilation or surgery may be required.

Zollinger–Ellison syndrome

This rare syndrome consists of a triad of non-β islet cell tumours of the pancreas that contain and release gastrin, gastric acid hypersecretion and severe ulcer disease. Extrapancreatic gastrinomas are also common and may be found frequently in the duodenal wall. A proportion of these patients have tumours of the pituitary gland and parathyroid gland (multiple endocrine neoplasia type I). Surgical resection of the gastrinoma may be curative. Medical management consists of greater than standard doses of PPIs. The somatostatin analogue octreotide is also effective but has no clear advantage over PPIs. Patients with idiopathic peptic ulcer disease should be investigated for Zollinger–Ellison syndrome and gastrinoma.

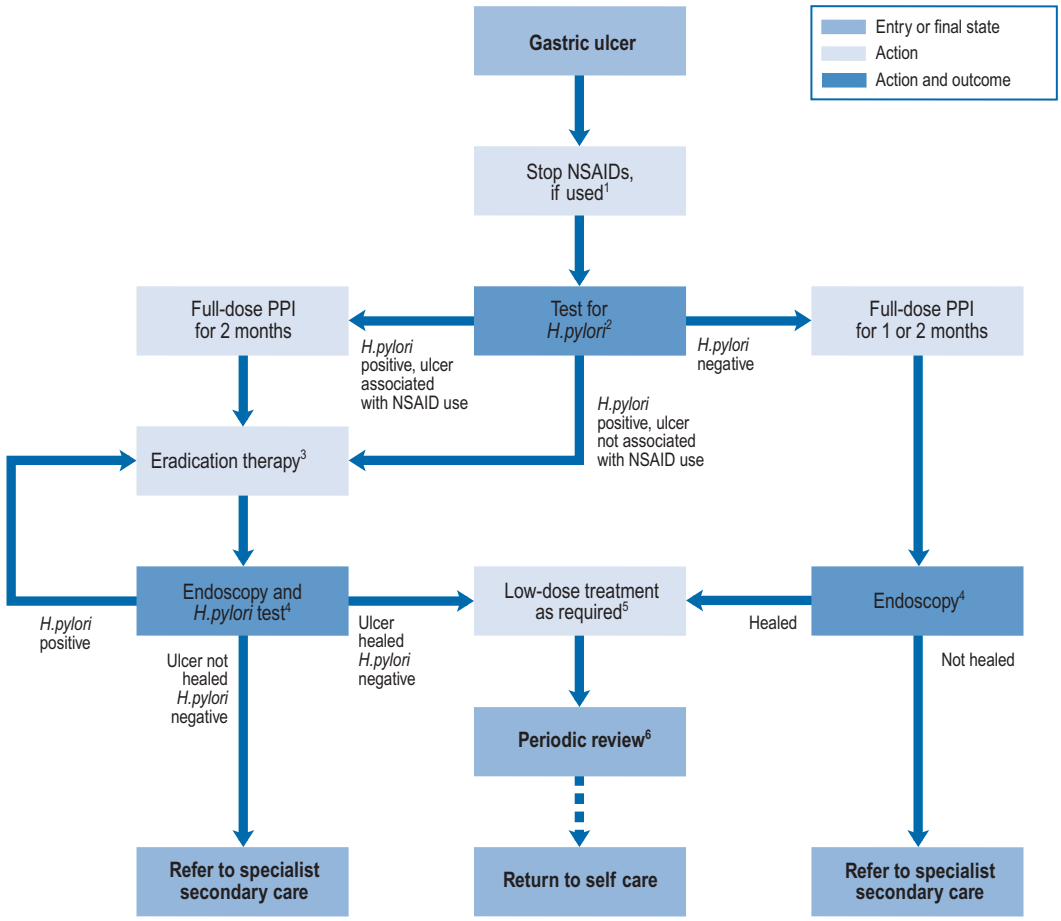
Stress ulcers

Severe physiological stress such as head injury, spinal cord injury, burns, multiple trauma or sepsis may induce superficial mucosal erosions or gastroduodenal ulcerations. These may lead to haemorrhage or perforation. Mechanical ventilation and the presence of coagulopathies place patients at particular risk of stress-related mucosal bleeding and may warrant prophylactic treatment (Quenot et al., 2009). Diminished blood flow to the gastric mucosa, decreased cell renewal, diminished prostaglandin production and, occasionally, acid hypersecretion are involved in causing stress ulceration. Intravenous acid-suppression therapy, histamine H_2-receptor antagonists and PPIs, and nasogastric tube

administration of sucralfate (4–6 g daily in divided doses) have been used to prevent stress ulceration in the intensive care unit until the patient tolerates enteral feeding. The most commonly used regimen is intravenous ranitidine 50 mg every 8 h reducing to 25 mg in severe renal impairment. Current evidence does not support routine use of prophylaxis and reports of complications associated with bacterial overgrowth in the gastro-intestinal tract in patients receiving acid suppressants should limit use only to those at high risk. Complications include association with hospital acquired *Clostridium difficile* diarrhoea (Dial et al., 2004) and pneumonia (Herzig et al., 2009).

Uncomplicated peptic ulcer disease

Treatment of endoscopically proven uncomplicated peptic ulcer disease has changed dramatically in recent years (Fig. 12.5A and B). Curing of *H. pylori* infection and discontinuation of NSAIDs are key elements for the successful management of peptic ulcer disease.



(A)

1 If NSAID continuation is necessary, after ulcer healing offer long-term gastric protection or consider substitution to a newer COX-2-selective NSAID.

2 Use a carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.

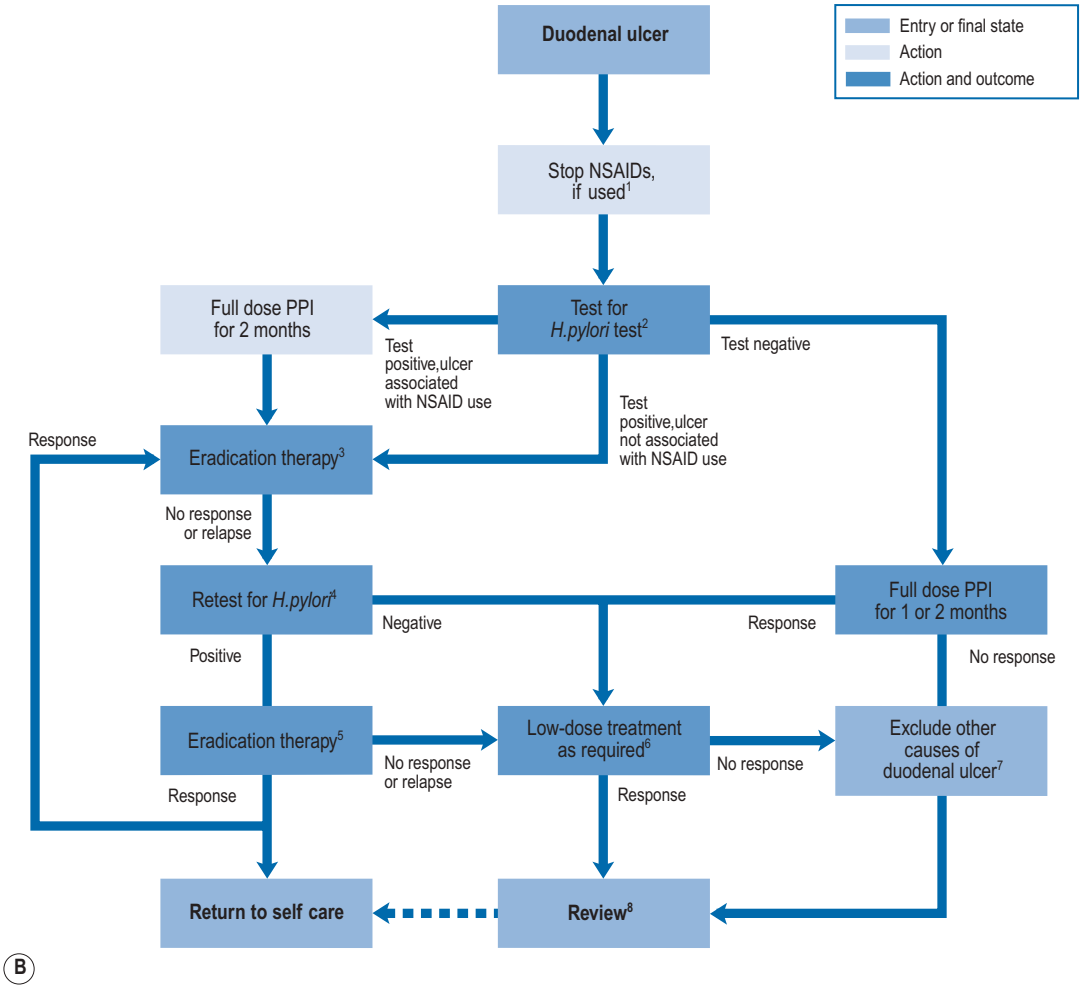
3 Use a proton pump inhibitor (PPI), amoxicillin, clarithromycin 500 mg (PAC_{500}) regimen or a PPI, metronidazole, clarithromycin 250 mg (PMC_{250}) regimen.
Follow guidance found in the *British National Formulary* for selecting second-line therapies.
After two attempts at eradication manage as *H. pylori* negative.

4 Perform endoscopy 6 to 8 weeks after treatment. If re-testing for *H.pylori* use a carbon-13 urea breath test.

5 Offer low-dose treatment, possibly used on an as-required basis, with a limited number of repeat prescriptions.

6 Review care annually, to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice. In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist.

Fig. 12.5 (A) Management algorithm for gastric ulcer.



1 If NSAID continuation is necessary, after ulcer healing offer long-term gastric protection or consider substitution to a newer COX-2-selective NSAID.
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3 Use a proton pump inhibitor (PPI), amoxicillin, clarithromycin 500 mg (PAC_{500}) regimen or a PPI, metronidazole, clarithromycin 250 mg (PMC_{250}) regimen.
4 Use a carbon-13 urea breath test.
5 Follow guidance found in the *British National Formulary* for selecting second-line therapies.
6 Offer low-dose treatment, possibly used on an as required basis, with a limited number of repeat prescriptions.
7 Consider: non-adherence with treatment, possible malignancy, failure to detect *H. pylori* infection due to recent PPI or antibiotic ingestion, inadequate testing or simple misclassification; surreptitious or inadvertent NSAID or asprin use; ulceration due to ingestion of other drugs; Zollinger-Ellison syndrome, Crohn's disease.
8 Review care annually, to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice.

Fig. 12.5, cont'd (B) Management algorithm for duodenal ulcer.

H. pylori eradication

It is known that *H. pylori* infection is associated with over 90% of duodenal ulcers and 80% of gastric ulcers. Cure of this infection with antibiotic therapy and simultaneous treatment with conventional ulcer-healing drugs facilitates symptom relief and healing of the ulcer and reduces the ulcer relapse rate. Antibiotics alone, or acid-suppressing agents alone, do not eradicate *H. pylori*. Both therapies act synergistically as growth of the organism occurs at elevated pH and antibiotic efficacy is enhanced during growth. Additionally, increasing intragastric pH may enhance antibiotic absorption. Recent studies limited to one country (Italy) suggest that sequential antibiotic treatment may be advantageous in overcoming emerging antibiotic resistance but the complexity of sequential regimens has the potential to affect adherence (Jafri et al., 2008)

High eradication rates are achieved by a short course of triple therapy consisting of a PPI, clarithromycin and amoxicillin or metronidazole in a twice-daily simultaneous regimen. European guidelines recommend 1 week of therapy, whereas the US guidelines recommend 10–14 days of therapy and achieve 7–9% better eradication rates (Malfertheiner et al., 2007).

Triple therapy consists of:

- OCA: omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g or
- OCM: omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg.

A lower dose of clarithromycin (250 mg twice daily) is effective and recommended when combined with metronidazole (NICE, 2004). However, some prescribers prefer to recommend 500 mg twice daily to achieve consistency and avoid prescribing errors.

Omeprazole may be replaced with any of the other PPI drugs. Local resistance rates determine the most appropriate first-line regimen, with OCA preferred in areas of high metronidazole resistance. In the UK, resistance to metronidazole has been reported in about 50% of *H. pylori* isolates, and resistance to clarithromycin in about 10%, although this is rising. Resistance to amoxicillin is rare. Sensitivity testing is of little value as *in vitro* resistance to either drug does not preclude eradication when those drugs are used as part of a triple therapy regimen. In patients with hypersensitivity to penicillin, the OCM regimen or substitution of amoxicillin from the OCA regimen with tetracycline 500 mg twice daily is used. If patients have recently received antibiotic treatment for any indication, a regimen avoiding that antibiotic is preferred.

Failure of a first-line regimen to achieve eradication will necessitate treatment with another triple therapy regimen or with a bismuth-based quadruple regimen. Recommended second-line triple therapy regimens include a PPI, amoxicillin or tetracycline and metronidazole. Most four-drug regimens contain bismuth subsalicylate, metronidazole, tetracycline or amoxicillin and a PPI and are generally not as well tolerated by patients as triple therapy regimens. Quadruple therapy may be used first-line where there is high prevalence of clarithromycin resistance. The indication should be reviewed in patients who are refractory to conventional as well as quadruple eradication therapies, to determine the importance of eradication before proceeding to endoscopic biopsies and determination of antibiotic sensitivity after culture. This strategy is rarely justified in dyspepsia.

Successful eradication relies upon patients adhering to their medication regimen. It is, therefore, important to educate patients about the principles of eradication therapy and also about coping with common adverse effects associated with their regimen. Diarrhoea is the most common adverse effect and should subside after treatment is complete. In rare cases, this can be severe and continue after treatment. If this happens, patients should be advised to return to their doctor as rare cases of antibiotic-associated colitis have been reported. If drugs are not taken as intended, then non-adherence may result in antibiotic resistance, should the antibiotic concentration at the site of infection decrease to a level where resistance may emerge.

If eradication is successful, uncomplicated active peptic ulcers heal without the need to continue ulcer-healing drugs beyond the duration of eradication therapy (Gisbert et al., 2004). Patients with persistent symptoms after eradication therapy should have their *H. pylori* status rechecked. This should be carried out no sooner than 4 weeks after discontinuation of therapy to avoid false-negative results due to suppression rather than eradication of the organism. If the patient is *H. pylori* positive, an alternative eradication regimen should be given. If eradication was successful but symptoms persist, gastro-oesophageal reflux or other causes of dyspepsia should be considered.

Patients who have had a previous gastro-intestinal bleed from a gastric ulcer should continue ulcer-healing therapy for a further 3 weeks in addition to eradication therapy. *H. pylori* eradication should be confirmed. The need for routine endoscopy to confirm ulcer healing is unclear but should be undertaken where malignancy is suspected.

Other accepted indications for *H. pylori* eradication include mucosal-associated lymphoid tissue (MALT) lymphoma of the stomach, severe gastritis, and in patients with a high risk of gastric cancer such as those with family history of the disease.

Treatment of NSAID-associated ulcers

NSAID-associated ulcers may be *H. pylori* positive. Although the presence of *H. pylori* may enhance the efficacy of acid suppression, eradication is generally recommended in infected patients with NSAID-associated ulcers as it is difficult to differentiate between *H. Pylori* or NSAID as the cause of the ulcer (Malfertheiner et al., 2009). If NSAIDs are discontinued, most uncomplicated ulcers heal using standard doses of a PPI, H_2-receptor antagonist, misoprostol or sucralfate. Healing is impaired if NSAID use is continued. Studies have demonstrated conflicting results, in terms of the comparative healing rates between PPIs and H_2-receptor antagonists, in this situation (Yeomans et al., 2006; Goldstein et al., 2007). PPIs demonstrate higher healing rates at 4 weeks but similar healing rates to H_2-receptor antagonists at 8 weeks. There is no evidence that high-dose PPI is better than treatment with the standard dose. Although effective, misoprostol use is limited by treatment-related adverse events.

Prophylaxis of NSAID ulceration

NSAIDs should be avoided in patients who are at risk of gastro-intestinal toxicity (see Box 12.1). However, some patients with chronic rheumatological conditions may require long-term NSAID treatment, in which case the lowest effective dose should be used. Dyspepsia is not a risk factor for ulcer complications but in those patients at high risk of ulcer complication, the NSAID should be stopped and investigation undertaken if dyspepsia develops.

Data suggests that *H. pylori* increases, has no effect on or decreases ulcer risk in NSAID users (Malfertheiner et al., 2007, 2009). The value of eradication of *H. pylori* in chronic NSAID users is, therefore, unclear but there may be some benefit in screening and eradicating *H. pylori* in patients about to start NSAIDs. The benefit is less apparent in those patients at low risk of peptic ulcer. In patients with a history of bleeding or non-bleeding ulcer, guidelines recommend screening for and eradicating *H. pylori* before starting low-dose aspirin (Bhatt et al., 2008). When using NSAIDs in patients with a previous bleeding ulcer, PPI maintenance therapy is more

effective secondary prophylaxis than *H. pylori* eradication alone, but a combination of both treatments is additive.

Treatment options for ulcer prophylaxis in patients at risk of peptic ulcer but who require NSAIDs, include co-therapy with acid-suppressing agents or a synthetic prostaglandin analogue, or substitution of a selective COX-2 inhibitor for a non-selective NSAID (Hooper et al., 2004). Comparison of study outcomes requires interpretation of whether ulcers are detected symptomatically or by endoscopy. The prostaglandin analogue, misoprostol at a dose of 800 µcg daily is effective at reducing NSAID-associated ulcer complications and symptomatic ulcers. Adverse effects, primarily diarrhoea, abdominal pain and nausea, limit its use as lower doses are less effective. PPIs are effective at reducing endoscopically diagnosed ulcers and dyspepsia symptoms but the effect on symptomatic ulcers is unclear. Studies have not demonstrated any advantage in using higher than standard doses of PPIs to reduce risk of ulcers. Standard doses of H_2-receptor antagonists are effective at reducing the risk of endoscopic duodenal ulcers. However, reduction in the risk of gastric ulcers requires double this dose. Gastroprotective agents licensed for prophylaxis of NSAID ulceration are listed in Table 12.1.

In low-dose aspirin users, standard-dose PPIs are more effective than high dose H_2-receptor antagonists in preventing recurrent ulcer bleeding following ulcer healing and eradication of *H. pylori* (Ng et al., 2010). However, in those patients who do not have a history of peptic ulcer bleeding, high-dose H_2-receptor antagonists might be an alternative to PPIs (Taha et al., 2009).

Given the contraindications to selective COX-2 inhibitors, their use is limited and further studies are required to clarify their place in minimising risk of ulcers in both primary and secondary prophylaxis. In patients with no history of peptic ulcer bleeding but with risk factors, a combination of COX-2 inhibitor with a PPI was similar in efficacy to a combination of non-selective NSAID with a PPI (Scheiman et al., 2006). In patients with a history of ulcer bleeding, a combination of selective COX-2 inhibitor with a PPI reduced recurrent ulcer bleeding compared to COX-2 inhibitor alone (Chan et al., 2007). This was not compared to a combination of a non-selective NSAID and a PPI. Although an earlier study suggested COX-2 inhibitors alone offered similar protection to that offered by a combination of non-selective NSAID with PPI (Lai et al., 2005), results suggest that in high-risk patients with a history of gastro-intestinal bleeding in whom an NSAID is indicated where alternative analgesic therapies have failed and in whom there are no contraindications to selective COX-2 inhibitors, a combination of PPI with a selective COX-2 inhibitor may be the safest strategy.

Table 12.1 Drugs for prophylaxis for NSAID-induced ulceration

Drug	Licensed indication	Prophylaxis dose
Omeprazole	Prophylaxis of further DU or GU	20 mg every day
Esomeprazole	Prophylaxis of DU or GU	20 mg every day
Lansoprazole	Prophylaxis of DU or GU	15–30 mg every day
Pantoprazole	Prophylaxis of DU or GU	20 mg daily
Misoprostol	Prophylaxis of DU or GU	200 µcg 2–4 times a day
Ranitidine	Prophylaxis of DU	150 mg twice a day
Ranitidine	Prophylaxis of DU (unlicensed)	300 mg twice day

DU, duodenal ulcer; GU, gastric ulcer.

H. pylori-negative, NSAID-negative ulcers

Ulceration in the absence of *H. pylori* infection or NSAID or aspirin use is rare and validation of negative medication history and *H. pylori* status should be confirmed using biopsy samples and a careful medication history including over the counter preparations. Many analgesics contain aspirin or NSAIDs and some patients purchase low-dose aspirin.

Gastro-oesophageal reflux disease

GORD is the term used to describe any symptomatic clinical condition or histopathological alteration resulting from episodes of reflux of acid, pepsin and, occasionally, bile into the oesophagus from the stomach (Moayyedi and Talley, 2006). Heartburn is the characteristic symptom, and the patient may also complain of acid regurgitation and dysphagia. Complications include oesophageal stricture, oesophageal ulceration and formation of specialised columnar-lined oesophagus at the gastro-oesophageal junction known as Barrett's oesophagus (Shaheen and Richter, 2009). The mechanism of acid reflux is multifactorial and involves transient lower oesophageal sphincter relaxations, reduced tone of the lower oesophageal sphincter, hiatus hernia and abnormal oesophageal acid clearance. The severity of inflammation of the oesophageal mucosa is described as categories of oesophagitis (Los Angeles A–D). However, approximately two-thirds of patients with GORD have normal mucosa on endoscopy. Hypersensitivity to normal acid exposure may be the cause of symptoms in this group of patients. Progression from non-erosive reflux disease to erosive oesophagitis and Barrett's oesophagus is rare.

Management of GORD focuses on symptom control rather than endoscopic findings, and therefore careful symptom evaluation is required (Box 12.5). Patients with alarm features or those who fail to respond to medical treatment should be referred for endoscopic investigation. *H. pylori* eradication is not recommended in the management of GORD (Malfertheiner et al., 2007).

Strategies for initial treatment include lifestyle measures such as weight loss and smoking cessation in combination

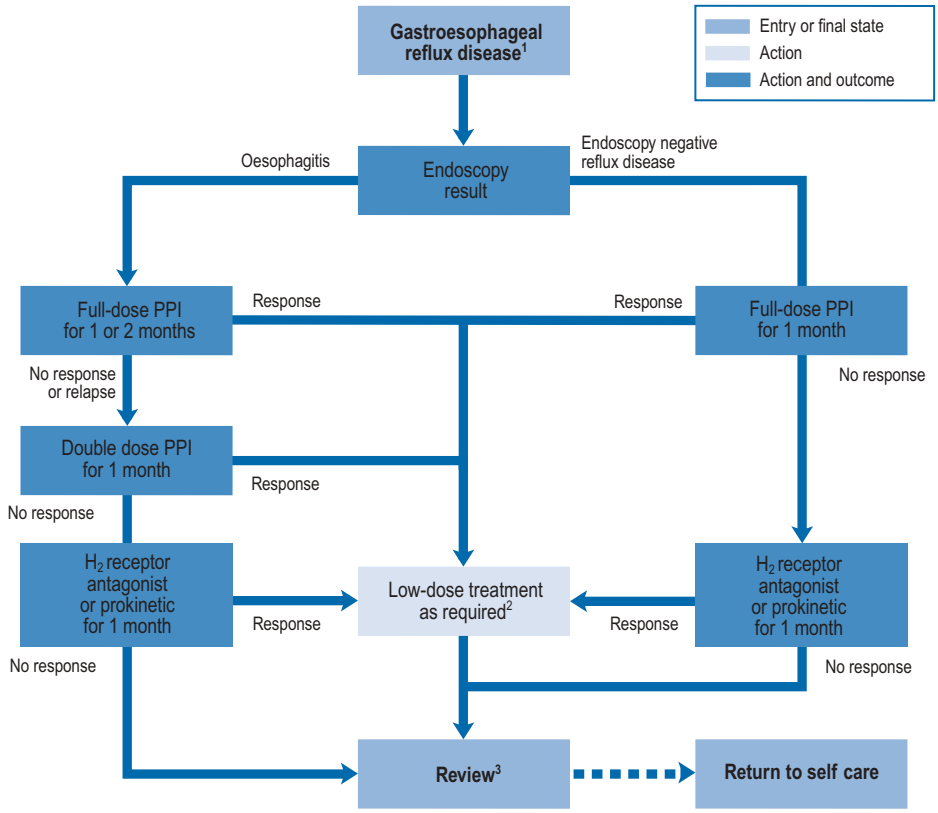
Box 12.5 Symptoms associated with gastro-oesophageal reflux disease

- Heartburn and regurgitation
- Belching
- Upper abdominal discomfort
- Bloating and postprandial fullness
- Chest pain
- Hoarseness
- Cough

with antacids. These measures may be effective in patients with no significant impairment of quality of life. When quality of life is impaired, acid-suppression therapy is the basis of effective treatment. A course of standard-dose PPI therapy is most effective for symptom relief, healing of oesophagitis and maintenance of remission in patients with GORD (Fig. 12.6).

Compared with erosive oesophagitis, there is a diminished response to acid suppression in non-erosive reflux disease but PPIs remain the most effective agents. Most patients respond after 4 weeks' treatment and after initial control of symptoms, therapy can be withdrawn. If symptoms return, intermittent courses can be given or, alternatively, on-demand single doses can be taken immediately as symptoms occur. Patients who relapse frequently may require continuous maintenance therapy using the lowest dose of acid suppression which provides effective symptom relief.

Escalating doses can be used in the small number of patients who do not respond to initial treatment. These patients should be investigated to confirm diagnosis. Those with a normal upper endoscopy may require pH monitoring or motility tests. Twice-daily dosing may be required in patients with persistent symptoms. A selected group of patients may benefit from anti-reflux surgery rather than the escalation of acid-suppressing



1 GORD refers to endoscopically determined oesophagitis or endoscopy-negative reflux disease. Patients with uninvestigated 'reflux-like' symptoms should be managed as patients with uninvestigated dyspepsia.
There is currently no evidence that *H. pylori* should be investigated in patients with GORD.

2 Offer low-dose treatment, possibly used on an as-required basis, with a limited number of repeat prescriptions.

3 Review long-term patient care at least annually to discuss medication and symptoms.
In some patients with an inadequate response to therapy or new emergent symptoms it may become appropriate to refer to a specialist for a second opinion.
A minority of patients have persistent symptoms despite proton pump inhibitor (PPI) therapy and this group remains a challenge to treat.
Therapeutic options include doubling the dose of PPI therapy, adding an H_2 receptor antagonist at bedtime and extending the length of treatment.

Fig. 12.6 Management algorithm for gastro-oesophageal reflux disease.

treatment. Patients with endoscopically severe oesophagitis (Los Angeles class C or D) should be kept on standard-dose PPIs long-term to maintain symptom relief and prevent the development of complications such as Barrett's oesophagus or oesophageal adenocarcinoma.

Ulcer-healing drugs

Proton pump inhibitors

The PPIs are all benzimidazole derivatives that control gastric acid secretion by inhibition of gastric H^+, K^+-ATPase, the enzyme responsible for the final step in gastric acid secretion from the parietal cell (Fig. 12.7).

The PPIs are inactive prodrugs that are carried in the bloodstream to the parietal cells in the gastric mucosa. The prodrugs readily cross the parietal cell membrane into the cytosol. These drugs are weak bases and therefore have a high affinity for acidic environments. They diffuse across the secretory membrane of the parietal cell into the extracellular secretory canaliculus, the site of the active proton pump (see Fig. 12.7). Under these acidic conditions the prodrugs are converted to their active form, which irreversibly binds the proton pump, inhibiting acid secretion. Since the 'active principle' forms at a low pH it concentrates selectively in the acidic environment of the proton pump and results in extremely effective inhibition of acid secretion. The different PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) bind to different sites on the proton pump, which may explain their differences in potency on a milligram per milligram basis.

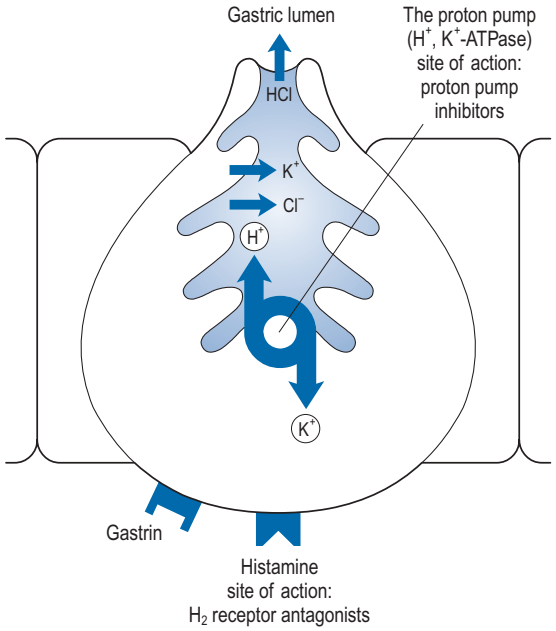


Fig. 12.7 Receptor stimulation of acid secretion.

PPIs require an enteric coating to protect them from degradation in the acidic environment of the stomach. This delays absorption and a maximum plasma concentration is reached after 2–3 h. Different formulations have been developed for patients with swallowing difficulties but these still rely upon some form of enteric coating (Table 12.2). New immediate-release formulations are under development which may overcome problems with enteric-coated granules blocking enteral feeding tubes.

Since these drugs irreversibly bind to the proton pump they have a sustained duration of acid inhibition which does not correlate with the plasma elimination half-life of 1–2 h. The apparent half-life is approximately 48 h. This prolonged duration of action allows once-daily dosing of PPIs, although twice-daily dosing is recommended in some cases of erosive oesophagitis or Barrett's oesophagus when a sustained gastric pH of greater than 4.0 is required. All PPIs are most effective if taken about 30 min before a meal as they inhibit only actively secreting proton pumps. Meals are the main stimulus to proton pump activity. The optimal dosing time is 30–60 min before the first meal of the day.

Intravenous PPIs are most frequently used to prevent recurrent ulcer bleeding in high-risk patients. Intravenous preparations are therapeutically equivalent to oral preparations. In the UK, omeprazole, pantoprazole and esomeprazole can be given intravenously.

Table 12.2 Available formulations of proton pump inhibitors

	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole
Capsule or tablet	√	√ (sucked)	√	√	√
Capsule granules can be dispersed in uncarbonated water or juice (pH < 5) or yoghurt	√				
Dispersible tablet	√	√			√
Granules for oral suspension					√
Intravenous	√		√		√
Available over the counter	√				

PPIs are metabolised in the liver to various sulphate conjugates that are extensively eliminated by the kidneys (80%). With the exception of severe hepatic dysfunction, no dose adjustments are necessary in liver disease or in renal disease. Apart from minor differences in bioavailability in the first few days of oral dosing, pharmacokinetics are similar among all PPIs. The antisecretory effect is also similar among all agents when administered chronically in equivalent standard doses.

Adverse drug reactions

Experience suggests that PPIs are a remarkably safe group of drugs. The most commonly reported side effects are diarrhoea, headaches, abdominal pain, nausea, fatigue and dizziness which resolve on drug discontinuation (Table 12.3). Possible mechanisms for diarrhoea include bacterial overgrowth, changes in intestinal pH and bile salt abnormalities. Diarrhoea is most commonly associated with lansoprazole, particularly in the elderly. Some cases of persistent chronic watery diarrhoea associated with lansoprazole have been diagnosed as microscopic colitis. This may be explained by the unique ability of lansoprazole to inhibit colonic proton pumps which may have an effect on colonic secretion and pH. Apart from the association between lansoprazole and diarrhoea, the incidence of adverse reactions is similar among the drugs in this group.

Loss of gastric acidity has been associated with colonisation of the normally sterile upper gastro-intestinal tract. Associations with increased risk of respiratory tract infections and *C. difficile*-associated disease have prompted more judicious use of PPIs. Long-term use may also decrease bone density and increase risk of hip fractures.

Drug interactions

The cytochrome P450 enzyme system is classified into a number of subgroups, several of which are involved in drug metabolism. All PPIs are metabolised to varying degrees by the same cytochrome P450 isoenzymes, CYP2C19 and CYP3A. All except rabeprazole are metabolised primarily via the CYP2C19 isoenzyme. This suggests rabeprazole may be less influenced by other drugs metabolised through this system or by genetic changes in hepatic metabolism. The affinity of individual PPIs for these enzymes influences the incidence of clinically relevant drug interactions.

- Pantoprazole has lower affinity for the enzyme system than the other PPIs and is also metabolised by a sulphotransferase which is non-saturable and not part of the cytochrome P450 system. Rabeprazole is also metabolised through a non-enzymatic pathway.
- Omeprazole inhibits CYP2C9 and 2C19, the isoenzymes involved in the metabolism of, for example, phenytoin (2C9), *S*-warfarin (2C9), diazepam (2C19) and *R*-warfarin (2C19). Omeprazole 40 mg daily can decrease the clearance of phenytoin, but phenytoin levels were unchanged after a dose of 20 mg of omeprazole daily. Therefore, phenytoin plasma concentrations should be monitored when omeprazole is taken concomitantly. Omeprazole may increase the coagulation time in patients receiving warfarin therapy, especially if doses higher than 20 mg daily are given. Changes in the plasma concentration of the less potent (*R*) enantiomer of warfarin have been observed; therefore, monitoring of the international normalised ratio (INR) is recommended during concomitant therapy. The metabolism of benzodiazepines, particularly diazepam, may be decreased by omeprazole. Similar interactions are likely with esomeprazole.
- Lansoprazole is a weak inducer of CYP1A2 and concurrent administration results in increased theophylline clearance.

Other isolated interactions have been reported:

- Omeprazole can increase the concentration of ciclosporin.
- Clarithromycin increases esomeprazole concentrations; however, omeprazole has also increased clarithromycin concentration.
- Lansoprazole has reduced the efficacy of the oral contraceptive pill.
- Clarithromycin has increased plasma lansoprazole concentration.
- Lansoprazole has increased plasma concentration of tacrolimus.
- Omeprazole has increased the concentration of escitalopram.
- Omeprazole has decreased renal elimination of methotrexate.

Approximately 3% of the Caucasian and 20% of the Asian population are poor metabolisers of PPIs due to genetic polymorphism associated with CYP2C19. High plasma concentrations are achieved and the relative capacity for metabolism by other isoenzymes may alter and result in drug interactions. In practice, the genotype of a patient is unknown. The relative contribution of CYP2C19 to PPI metabolism is greatest with omeprazole and least with rabeprazole. The observation of decreased clopidogrel activity and increased cardiovascular events has been linked to competitive inhibition of CYP2C19 possibly caused by concomitant treatment with PPIs.

Table 12.3 Common adverse reactions to ulcer-healing drugs

Proton pump inhibitors	H_2-receptor antagonists	Sucralfate
Diarrhoea	Diarrhoea	Constipation
Headache	Headache	
Abdominal pain	Abdominal pain	
Nausea	Confusion	
Fatigue		
Dizziness		

The use of symptom-driven, on-demand PPI therapy may prove problematic if used concomitantly with warfarin or phenytoin. Careful monitoring should be undertaken. All acid-suppressing drugs potentially decrease the absorption of some drugs by increasing gastric pH. Reduction in absorption of ketoconazole and increased absorption of digoxin have been reported with PPIs. The absorption of drugs formulated as pH-dependent, controlled-release products may also be altered. Very few clinically important drug interactions have been reported despite the widespread use of these agents.

Clinical use

PPIs relieve symptoms and heal peptic ulcers faster than H_2-receptor antagonists. They also heal ulcers that are refractory to H_2-receptor antagonists. All PPIs provide similar *H. pylori* eradication rates and ulcer healing when used at their recommended doses. Standard doses of PPIs are used concomitantly with non-selective NSAIDs and with low-dose aspirin in patients at risk of peptic ulcers or ulcer bleeding. High dose intravenous PPIs are used to prevent recurrent bleeding in high-risk patients (active bleeding or non-bleeding visible vessel) during the initial 72 h after a bleed. In GORD, PPIs heal oesophagitis and control symptoms more rapidly than H_2-receptor antagonists. Differences between PPIs in terms of speed of symptom relief are observed only in the first few days of treatment. Patients with severe oesophagitis should continue long-term PPI therapy, whereas those with milder GORD should be stepped down in terms of acid suppression and therapy withdrawn if symptoms are controlled. On-demand therapy is used to maintain symptom control. Patients with functional dyspepsia should not routinely receive long-term treatment with PPIs. PPIs can be purchased over the counter for short-term relief of heartburn.

H_2-receptor antagonists

The H_2-antagonists are all structural analogues of histamine. They competitively block the histamine receptors in gastric parietal cells, thereby preventing acid secretion. Pepsinogen requires acid for conversion to pepsin and so when acid output is reduced, pepsin generation is, in turn, also reduced.

All the available drugs (cimetidine, ranitidine, famotidine, nizatidine) have similar properties. Maximum plasma concentration is reached within 1–3 h after administration. First-pass hepatic metabolism varies, ranitidine being most extensively metabolised which explains the difference between the intravenous and oral dose. All H_2-antagonists are eliminated to a variable and significant extent via the kidneys, and all require dosage reduction in moderate-to-severe renal impairment. They are equally effective at suppressing daytime and nocturnal acid secretion while they do not cause total achlorhydria. The evening dose of a H_2-antagonist is particularly important because during the daytime, gastric acid is buffered for long periods by food; however, during the night this does not occur and the intragastric pH may fall below 2.0 for several hours. For healing oesophagitis, intragastric pH must remain above 4.0 for 18 h or more per day. H_2-receptor antagonists are, therefore, not effective in healing oesophagitis. Adding a bedtime dose of H_2-receptor antagonist to PPI therapy may enhance nocturnal gastric pH control in patients in whom nocturnal gastric acid breakthrough is problematic.

The role of H_2-receptor antagonists in the management of peptic ulcer disease has diminished. H_2-receptor antagonists are less effective than PPIs in eradication regimens, in treating ulcers when NSAIDs are continued, and in prophylaxis of NSAID-induced ulcers. H_2-receptor antagonists do effectively heal ulcers in patients who discontinue their NSAID and they also have a role in continuing acid suppression for symptomatic treatment following eradication therapy. Their main role is in the empirical management of dyspepsia symptoms. If patients with mild symptoms gain adequate relief, it is not necessary to use a PPI. H_2-receptor antagonists are preferred over PPIs in the second-line treatment of heartburn in pregnancy, although there is growing evidence to support safe use of PPIs in those not controlled by H_2-receptor antagonists. H_2-receptor antagonists can be purchased in doses lower than those prescribed for the management of heartburn and indigestion.

Adverse drug reactions

H_2-receptor antagonists are a remarkably safe group of drugs with a lower risk of side effects than PPIs. The risk of any adverse reaction is below 3% and serious adverse reactions account for less than 1%. Diarrhoea and headache are the most common and occasionally mental confusion and rashes have been reported (see Table 12.3). Hepatotoxicity is a rare adverse effect. Cimetidine, due to its antiandrogenic effects, has been associated with gynaecomastia and impotence when used in high doses.

Drug interactions

Although many drug interactions have been suggested with cimetidine, many have only been demonstrated *in vitro* and are of doubtful clinical significance. Cimetidine inhibits the activity of cytochrome P450 and consequently retards oxidative metabolism of some drugs. This interaction is potentially important for drugs with a narrow therapeutic index. The clearance of theophylline is reduced to about 40% of normal, and raised plasma levels occur as a result. Phenytoin metabolism is reduced, and toxicity is theoretically possible. The metabolism of a number of benzodiazepines, including diazepam, flurazepam and triazolam, is impaired and levels are raised.

The interaction with warfarin has frequently been cited as justification to change to an alternative H_2-antagonist which binds less intensively to the CYP 450 system; however, careful investigation has shown that this interaction is complex. The metabolism of (*R*)-warfarin is affected to a greater degree than that of (*S*)-warfarin. As the (*S*) enantiomer is the more potent, the pharmacodynamic effects of the interaction may be modest, although the plasma warfarin concentrations may be increased. Current opinion suggests that warfarin may safely be added with appropriate monitoring when patients are already taking cimetidine in regular daily doses. Other H_2-antagonists should be used in patients who are difficult to stabilise on warfarin or for whom frequent monitoring is not feasible.

All acid-suppressing drugs potentially decrease the absorption of drugs such as ketoconazole and other pH-dependent controlled-release products by increasing gastric pH.

Bismuth chelate

Bismuth has been included in antacid mixtures for many decades but fell from favour because of its neurotoxicity. Bismuth chelate is a relatively safe form of bismuth that has ulcer-healing properties comparable to those of H_2-antagonists. Its mode of action is not clearly understood but it is thought to have cytoprotective properties. Bismuth is toxic to *H. pylori* and was one of the first agents to be used to eradicate the organism and reduce ulcer recurrence. Tripotassium dicitratobismuthate in combination with tetracycline, metronidazole and a PPI is used in quadruple therapy regimens in patients resistant to triple therapy.

Adverse drug reactions

Small amounts of bismuth are absorbed from bismuth chelate, and urinary bismuth excretion may be raised for several weeks after a course of treatment. The risks of bismuth intoxication are small if these products are used at the recommended dose and for short courses of treatment. Bismuth may accumulate in patients with impaired renal function. The most commonly reported events are nausea, vomiting, blackened tongue and dark faeces.

Sucralfate

Sucralfate is the aluminium salt of sucrose octasulphate. Although it is a weak antacid, this is not its principal mode of action in peptic ulcer disease. It has mucosal protective effects including stimulation of bicarbonate and mucus secretion and stimulation of mucosal prostanoids. At pH less than 4.0 it forms a sticky viscid gel that adheres to the ulcer surface and may afford some physical protection. It is capable of adsorbing bile salts. These activities appear to reside in the entire molecular complex and are not due to the aluminium ions alone. Sucralfate has no acid-suppressing activity. At a dose of 2 g twice daily, sucralfate is effective in the treatment of NSAID-induced duodenal ulcers, if the NSAID is stopped. However, it is not effective in the treatment and prevention of NSAID-related gastric ulcers. It has also been used in the prophylaxis of stress ulceration. The liquid formulation is often used as the tablets are large and difficult to swallow.

Adverse drug reactions

Constipation appears to be the most common problem with sucralfate, and this is thought to be related to the aluminium content (see Table 12.3). About 3–5% of a dose is absorbed, and therefore there is a risk of aluminium toxicity with long-term treatment. This risk is correspondingly greater in patients with renal impairment. Caution is required to avoid oesophageal bezoar formation around a nasogastric tube in patients managed in the intensive care unit.

Drug interactions

Sucralfate may bind to other agents in the gastro-intestinal tract and reduce the absorption of other drugs. Therefore, it should be taken at least 2 h following other medicines.

Antacids

Antacids have a place in symptomatic relief of dyspepsia, in particular symptoms associated with GORD. They have a role in the management of symptoms which sometimes remain for a short time after *H. pylori* eradication of uncomplicated duodenal ulcer.

The choice of antacid lies between aluminium-based and magnesium-based products, although many proprietary products combine both. Calcium-based products are unsuitable as calcium stimulates acid secretion. Antacids containing sodium bicarbonate are unsuitable for regular use because they deliver a high sodium load and generate large quantities of carbon dioxide. It should be noted that magnesium trisilicate mixtures contain a large amount of sodium bicarbonate. Some products contain other agents such as dimeticone or alginates. Products containing sodium alginate with a mixture of antacids are effective in relief of symptoms in GORD but are not particularly effectual antacids.

Aluminium-based antacids cause constipation, and magnesium-based products cause diarrhoea. When combination products are used, diarrhoea tends to predominate as a side effect. Although these are termed 'non-absorbable', a proportion of aluminium and magnesium is absorbed and the potential for toxicity exists, particularly with coexistent renal failure.

Antacids provide immediate symptom relief and a more rapid response is achieved with liquid preparations. They have a limited duration of action and need to be taken several times a day, usually after meals and at bedtime. Administration should be separate from drugs with potential for chelation, such as tetracycline and ciprofloxacin, and also pH-dependent controlled-release products.

Patient care

Patient education

Patients who present with symptoms of dyspepsia should be assessed in terms of risk of serious disease. Referral for investigation is indicated if they exhibit alarm features. Patients with predominant reflux-like symptoms are likely to respond to antacid/alginate medicines. In those with reflux-like symptoms, lifestyle should be assessed as weight loss is known to improve reflux symptoms in obese patients and raising the head of the bed may improve nocturnal symptoms of heartburn. A medication history, including purchased medicines, should be undertaken to identify likely or possible drug-induced causes of symptoms. Symptoms of dyspepsia are associated with many medicines including aspirin, NSAIDs and corticosteroids. Other agents are associated with gastro-oesophageal reflux and include those with antimuscarinic

effects, for example, tricyclic antidepressants, or those which relax muscle tone, for example, calcium channel blockers and nitrates, or those which cause oesophageal mucosal damage, for example, biphosphonates. Clinical medication review allows assessment of the benefits and risks associated with medicines and referral to the prescriber may be necessary. Patients who do not respond to 2 weeks of symptomatic relief medication should be referred to the primary care doctor.

Patients should be advised to seek the pharmacist's advice when purchasing over-the-counter analgesic preparations. Patients with risk factors for peptic ulcer disease should be advised to avoid over-the-counter aspirin and NSAIDs and to use paracetamol-based products. Taking aspirin or NSAIDs with or after food may decrease the risk of dyspepsia symptoms but does not decrease the risk of ulcer complications. Before prescribing NSAID or aspirin therapy, patients should be assessed in terms of both cardiovascular and gastro-intestinal risk. Benefits must outweigh risks in NSAID users and if NSAIDs are necessary in those at risk of ulcer complications, prophylaxis should be prescribed. Consideration should be given to screening for *H. pylori*. Patients should be aware of the optimum time of administration of PPIs, the dose and duration of therapy. Misoprostol should not be used in pregnant women, and women of childbearing age should be warned appropriately.

Patients with diagnosed peptic ulcer disease need to be educated about the current principles of therapeutic management determined by the diagnosis and, if appropriate, the balanced risks associated with continued aspirin or NSAID therapy. Uncomplicated disease requires a short course of treatment which may or may not include eradication of *H. pylori*. Patients need to know the importance of adherence to eradication therapy for successful treatment and to avoid development of resistance to antibiotics. Previous adverse reactions should be established; for example, patients who are sensitive to penicillin need an eradication regimen which does not include amoxicillin. Patients should be warned of the specific side effects to be expected from the regimen chosen for them and advised what to do should they experience any of these effects. Patients taking metronidazole must avoid alcohol as they might have a disulfiram-like reaction with sickness and headache. Patients also need to know how their therapy will be followed up. In most patients, a single treatment course is required and there is no need for maintenance therapy unless they require prophylaxis treatment to reduce risks associated with continued NSAID or low-dose aspirin therapy.

Patient monitoring

Treatment success in uncomplicated peptic ulcer disease is measured by review of the patient in terms of symptom control. Patients with complicated ulcers or those who continue to have symptoms will receive a urea breath test and/or an endoscopy to confirm successful eradication of *H. pylori*. Very few patients require follow-up endoscopy. Patients should be aware of what their review will entail and when their review will take place. If patients comply with their medication the review process may be kept to a minimum.

Following eradication therapy, some patients continue to experience symptoms of abdominal pain. Patients should be reassured that these symptoms will resolve spontaneously, but if necessary an antacid preparation can be recommended to relieve symptoms until review. Patients receiving treatment for NSAID-induced ulceration should continue their ulcer-healing therapy for 4 weeks. If the NSAID or aspirin has been discontinued there is no need to continue ulcer treatment therapy once the ulcer has healed unless the NSAID or aspirin must also be continued.

Patients with iron-deficiency anaemia following a bleeding ulcer may be prescribed oral iron therapy. If patients suffer side effects such as constipation or diarrhoea, the dose of iron should be reduced. Treatment with iron should be for at least 3 months. Iron preparations are best absorbed from an empty stomach but if gastric discomfort is felt, the preparation should be taken with food.

Some common therapeutic problems in the treatment of peptic ulcer disease are summarised in Table 12.4.

Table 12.4 Common therapeutic problems in peptic ulcer disease

	Comments
Ulcer-like symptoms of dyspepsia are not specific for peptic ulcer disease and are often present in functional (non-ulcer) dyspepsia	Predominant heartburn differentiates GORD from dyspepsia. Patients with GORD are likely to respond to antisecretory therapy
In uncomplicated patients with ulcer-like symptoms of dyspepsia, there is controversy about whether a 1-month course of acid suppression or test and for *H. pylori* should be carried out initially	Identification and eradication of *H. pylori* will benefit those with ulcers and a small proportion of *H. pylori*-positive patients with functional dyspepsia. A course of acid suppression will have similar outcomes but ulcers may relapse. Eradication of *H. pylori* plays no role in management of GORD
A test and treat policy is cost-effective compared with initial endoscopy in patients with uncomplicated dyspepsia	There is no evidence to support widespread eradication of *H. pylori* in primary care
Patients on proton pump inhibitors (PPIs) can have false-negative results for *H. pylori*	PPIs should be withdrawn at least 2 weeks before urea breath test or biopsy urease testing (endoscopy)

Continued

Table 12.4 Common therapeutic problems in peptic ulcer disease—cont'd

	Comments
Following a 7-day eradication therapy regimen, antisecretory therapy can normally be stopped	Longer courses of acid-suppressive therapy should be reserved for patients with active ulcers complicated by bleeding and/or NSAID use
First-line eradication therapy comprises twice-daily PPI, amoxicillin 1 g and clarithromycin 500 mg	Metronidazole can be substituted in those patients allergic to amoxicillin and for second-line therapy. When combined with metronidazole, the dose of clarithromycin can be reduced to 250 mg
Use of high dose intravenous PPIs	Intravenous PPI use is not recommended before endoscopic diagnosis in gastro-intestinal bleeding. High dose intravenous PPI is recommended for 72 h after endoscopic haemostatic therapy in patients at high risk of re-bleeding from peptic ulcer
In patients with NSAID-associated active peptic ulcer disease who test positive for *H. pylori*, the cause of the ulcer may not be confirmed	The ulcer should be healed with a PPI for 4 weeks and *H. pylori* eradicated. Eradication of *H. pylori* reduces the risk of recurrent bleeding
The treatment of NSAID-associated ulcers may differ depending upon whether or not the NSAID must be continued	If NSAIDs are withdrawn, healing rates at 4 weeks are best with PPIs and are similar between H_2-receptor antagonists and PPIs after 8 weeks. PPIs are continued only if NSAIDs are continued
Patients in whom low-dose aspirin is indicated but have risk factors for peptic ulcer disease	Use of aspirin should be considered carefully, especially for primary prophylaxis of cardiovascular disease. Enteric coating does not reduce this risk. Clopidogrel is not a safer alternative than aspirin in combination with a PPI
There is an increased risk of bleeding with dual antiplatelet therapy	PPIs are thought to decrease conversion of clopidogrel to active metabolite, thus decreasing efficacy of clopidogrel. If dual antiplatelet therapy is indicated after PCI, use H_2 receptor antagonist unless high risk (previous gastro-intestinal bleed), when PPI indicated
NSAID use in elderly patients	Patients over 65 years of age are at increased risk of peptic ulcer disease associated with NSAIDs and often present with 'silent ulcers'. NSAIDs (prescription and non-prescription) should be avoided in the elderly
Patients who are candidates for COX-2 inhibitors	COX-2 inhibitors are associated with less gastro-intestinal toxicity than non-selective NSAIDs. COX-2 inhibitors are contraindicated in cardiovascular disease. The reduction in gastro-intestinal risk associated with COX-2 inhibitors is similar to reduction in risk associated with non-selective NSAIDs in combination with gastroprotective agents
Criteria and regimens to administer for stress ulcer prophylaxis are unclear	Intravenous H_2-receptor antagonist therapy is given to patients at risk until enteral feeding is tolerated. Definite risk factors include mechanical ventilation, presence of coagulopathy and spinal cord injury. Controversial risks include head injury, sepsis, burns, multiple trauma, steroid therapy
Patients who require long-term PPI therapy	Those in whom long-term NSAIDs or low-dose aspirin are indicated and who have risk factors for associated upper gastro-intestinal complications. Patients with endoscopically diagnosed GORD who either have severe erosive oesophagitis or severe symptoms which can only be controlled with maintenance therapy

PCI, percutaneous coronary intervention.

Case studies

Case 12.1

A 62-year-old man (Mr BD) presented to A&E following haematemesis and melaena. He suffered no pain. His past medical history included non-ST-elevated myocardial infarction (NSTEMI) for which he had undergone percutaneous coronary intervention (PCI) and bare metal stent insertion 4 months previously. Mr BD stopped smoking 2 years previously, drinks alcohol in moderation and is not obese. He was taking the following prescribed medicines:

Aspirin (dispersible) 75 mg
Clopidogrel 75 mg
Ramipril 2.5 mg twice daily
Simvastatin 40 mg daily
Atenolol 100 mg
GTN spray prn

On investigation Mr BD's haemoglobin concentration was 8 g/dL (11.5–16.5 g/dL) with an MCV of 90 fL (83–101 fL). His blood pressure was 98/60 mmHg with a heart rate of 120 beats per minute and respiratory rate of 20 beats per minute. There was no jaundice or stigmata of liver disease. Plasma urea was 18 mmol/L (3.1–7.9 mmol/L) with a creatinine of 87 µmol/L (75–155 µmol/L). INR was 1.0. Serum sodium was 142 mmol/L (135–145 mmol/L) and serum potassium was 4.3 mmol/L (3.4–5.0 mmol/L). Endoscopy revealed an actively bleeding gastric ulcer.

Questions

1. What immediate treatment should Mr BD receive?
2. What treatment should he receive at the time of endoscopy?
3. Why should biopsies be taken at the time of endoscopy?
4. What pharmacological treatment should be given to reduce the risk of re-bleeding following endoscopic haemostatic therapy?
5. What was the likely cause of the bleeding ulcer?
6. When should antiplatelet therapy be restarted and with which agent(s)?
7. Is gastroprotection indicated following ulcer healing?
8. Summarise Mr BD's educational needs in terms of his medicines.

Answers

1. Mr BD's age, comorbidity and clinical signs of shock place him at risk of death and in need of emergency hospital admission for aggressive resuscitation with intravenous fluids and red cell transfusion. Either colloid or crystalloid solutions can be used for volume restoration prior to administering blood products. Sodium chloride 0.9% is appropriate fluid replacement. Following resuscitation, early endoscopic examination should be undertaken, within 24 h of presentation. There is no evidence to support the use of intravenous PPIs prior to diagnosis by endoscopy. The most frequent cause of upper gastro-intestinal bleeding is peptic ulcer disease. If Mr BD is nauseated, an antiemetic should be prescribed.
2. The clinical markers suggest urgent endoscopy is indicated. Patients who are shocked and have active peptic ulcer bleeding are at high risk of continuing to bleed and should receive haemostatic endoscopic therapy. Endoscopic treatment is indicated only for those with high-risk lesions (active bleeding, non-bleeding visible vessels or adherent blood clot). Endoscopic injection of large volume (at least 13 mL) 1:10,000 adrenaline achieves haemostasis through vasoconstriction and haemostasis is sustained if this is combined with thermal coagulation or mechanical endoscopic clipping. The patient should receive combination endoscopic therapy.
3. The presence of *H. pylori* should be sought at the time of endoscopy. Biopsies should be taken from the antrum and the body of the stomach. Samples are sent for testing for the presence of malignant cells and samples are used for the rapid urease test for *H. pylori*. The presence of bleeding may reduce the sensitivity of the rapid urease test and if negative results are obtained, a urea breath test can be undertaken once oral intake is established.
4. In high-risk patients who have received endoscopic haemostatic therapy, high dose intravenous PPI therapy reduces the risk of re-bleeding. The optimum dose and route is unclear but improved mortality is observed in high-risk patients when a dose of 80 mg bolus followed by 8 mg/h infusion for 72 h is given. Maintaining intragastric pH above 6 is considered to stabilise clot formation and prevent re-bleeding.

   If a positive test for *H. pylori* was obtained, oral eradication therapy should be given, although there is no evidence to suggest this must be given in the acute phase so should wait until oral intake is established. *H. pylori* eradication therapy is effective in prevention of re-bleeding from peptic ulcer. Ulcer healing can be achieved with an additional 3 weeks treatment with standard-dose PPI.
5. Mr BD was taking dual antiplatelet therapy to reduce the risk of myocardial infarction and cardiovascular death. These agents act synergistically through different pathways. Aspirin is a thromboxane A_2 inhibitor and clopidogrel is an adenosine diphosphate (ADP) inhibitor. Both these agents carry an increased risk of bleeding events, the risk being additive with dual therapy. Mr BD did not have any additional risk factors for peptic ulcer disease but it is important to take a careful medication history to identify if he had been taking NSAID analgesics and ensure he avoids such medicines in the future. The bleeding peptic ulcer was likely caused by the combination of aspirin and clopidogrel.
6. In patients with NSTEMI, most benefit is gained from the addition of clopidogrel to aspirin therapy in the first 3 months. Prolonged treatment for 12 months is indicated if a drug-eluting stent is inserted but as this patient had a bare metal stent inserted 4 months previously, the benefit from the addition of clopidogrel does not outweigh the gastro-intestinal bleeding risk and consideration should be given to discontinuation of clopidogrel. Aspirin should be continued at a dose of 75 mg daily. There is no evidence to suggest enteric coating is of any benefit, so the dispersible formulation should be continued. It is suggested that aspirin should be restarted within 7 days of discontinuation to maintain cardiovascular secondary prevention.
7. Standard dose of PPI should be continued as maintenance therapy in this patient to reduce the risk of further aspirin induced gastro-intestinal bleeding.
8. Mr BD needs to be aware of both his cardiovascular and gastro-intestinal risks. He does need to continue aspirin but he should be aware of the need to discontinue clopidogrel now as it is 4 months following his NSTEMI and the benefit does not outweigh the risk. He should not to take any other aspirin or NSAID containing medicines.

   Mr BD should be prescribed 7 days treatment with twice-daily omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg after ascertaining he is not penicillin sensitive. The importance of this treatment in prevention of re-bleeding should be emphasised to encourage adherence to the prescribed course which he may complete after discharge from hospital. Aspirin will be restarted and the dose of omeprazole will be reduced to 20 mg daily. A repeat endoscopy will be undertaken only if malignancy was suspected. Mr BD will return for a breath test to confirm eradication of *H. pylori*, although there is a risk of a false-negative result with concomitant omeprazole therapy.

   The anaemia associated with the acute bleed was treated with a blood transfusion and should not require additional oral iron therapy which is indicated in the case of microcytic anaemia more commonly caused by chronic bleeding

Case 12.2

A 57-year-old woman (Mrs MG) presents with symptoms of epigastric pain which has interfered with her normal activities over the previous few weeks. Medication history reveals that Mrs MG takes no prescribed medicines and occasional paracetamol as an analgesic for minor ailments. Although she has occasional heartburn, this is not the predominant symptom. Mrs MG has not vomited and does not have difficulty or pain on swallowing. She has not lost weight recently and has normal stools with no evidence of bleeding. The pain is not precipitated by exercise and does not radiate to the arms and neck. Mrs MG is a non-smoker and only takes a small quantity of alcohol on social occasions. She has an allergy to penicillin.

Questions

1. How should Mrs MG be treated?
2. Which *H. pylori* test should be used in primary care?

Answers

1. It is important to ascertain if Mrs MG has alarm features which should be investigated particularly as her age places her at higher risk of gastro-intestinal cancer. However, cancer is very rare in the absence of alarm features, and therefore initial management strategies are suggested prior to referral for investigation. Symptom assessment also suggests the pain is not cardiac in nature. Most patients with ulcer-like epigastric pain have functional dyspepsia but a small proportion have peptic ulcer disease. Her symptoms are affecting her quality of life, so an initial strategy of testing for *H. pylori* would be appropriate and if positive a 7-day course of twice-daily eradication therapy of omeprazole 20 mg, metronidazole 400 mg and clarithromycin 250 or 500 mg can be prescribed. Mrs MG should be advised to complete the course of therapy to avoid eradication failure and/or resistance to antibiotics. The potential interaction between metronidazole and alcohol should be explained to the patient in terms of the risk of nausea, vomiting, flushing and breathlessness which may occur during and for a few days after discontinuing metronidazole. Patients should also be alerted to the common adverse effect of diarrhoea associated with triple therapy. Patients should be encouraged to cope with the inconvenience but report symptoms to their doctor if they continue after the course of treatment is finished. If Mrs MG has an uncomplicated ulcer, it should heal with this treatment and if she has functional dyspepsia, a small proportion of patients obtain symptom relief. If Mrs MG tests negative for *H. pylori*, a 4-week course of standard-dose PPI can be given for symptomatic relief. If symptoms persist despite eradication therapy, successful eradication should be confirmed 4 weeks after treatment and eradication repeated if necessary. If patients over 55 years of age do not respond to either of these initial management strategies, referral for further investigation should be undertaken.
2. The most accurate non-invasive *H. pylori* test is the carbon-13 urea breath test. Alternative tests are the stool antigen test and a laboratory-based serology test. Local facilities and costs determine the choice of tests. Serology tests based on measurement of serum antibody are commonly used for initial detection of *H. pylori* but cannot be used to confirm eradication since circulating antibody remains for several weeks after removal of antigen.

Case 12.3

A 68-year-old woman (Ms WR) presents for review of her medication. Her medical history includes hypertension and osteoarthritis of the knees. Ms WR receives a regular prescription for:

Bendroflumethiazide 2.5 mg
Naproxen 500 mg twice daily

Ms WR stopped smoking 4 years previously and drinks no more than 10 units of alcohol per week. She is overweight with a BMI of 30 kg/m². Ms WR occasionally purchases an antacid to treat symptoms of heartburn if she's eaten a large meal at night. Her blood pressure was 148/92 mmHg with a pulse of 82 beats per minute.

Routine blood tests revealed:

		Reference range
Sodium	**138 mmol/L**	**135–145 mmol/L**
Potassium	**3.9 mmol/L**	**3.4–5.0 mmol/L**
Creatinine	**110 µmol/L**	**75–155 µmol/L**
Blood glucose	**6.8 mmol/L**	**<11.1 mmol/L**
Total cholesterol	**4.5 mmol/L**	**<4.0 mmol/L**
Haemoglobin	**12.0 g/dL**	**11.5–16.5 g/dL**

Questions

1. What is the mechanism for NSAID-induced peptic ulcer disease?
2. What are the risks associated with NSAID use in this patient?
3. What are the options for treating her pain and minimising the risk of peptic ulceration?

Answers

1. NSAIDs cause superficial erosions, but the main mechanism for causing ulcers in through their systemic inhibition of mucosal prostaglandin production. COX-1 is the enzyme responsible for synthesis of prostaglandins responsible for gastro-intestinal mucosal protection through maintenance of blood flow and production of mucus and bicarbonate. Another isoform of COX, COX-2 is involved in the inflammatory response and the prostaglandins produced are associated with pain and inflammation. The anti-inflammatory action of NSAIDs is thought to be as a result of inhibition of COX-2. Inhibition of COX-1 is thought to be responsible for the gastro-intestinal and renal adverse effects of NSAIDs.
2. Age-related reduction in the synthesis of prostaglandins and secretion of bicarbonate from the gastro-intestinal mucosa is the probable reason for the age-related increase in incidence of peptic ulcer bleeding. Patients over 60 years of age are at higher risk of peptic ulcer complications than their younger counterparts and the risk is much higher in those above 75 years of age. Other risk factors include a previous history of peptic ulcer disease, in particular peptic ulcer bleeding. Dyspepsia symptoms do not correlate with those who develop peptic ulcer disease and are, therefore, not a risk factor and can be treated symptomatically. Concomitant drug therapy such as aspirin, corticosteroids and anticoagulants increase the risk of peptic ulcer complications. In this case, the patient's age places her at risk, and therefore the benefits of the NSAID should be weighed against the risks and potential options for risk management considered.

   Age is also a risk factor for NSAID-induced decrease in renal perfusion caused by inhibition of prostaglandin-stimulated renal blood flow, a compensatory mechanism which is activated when renal perfusion is impaired. Withdrawal of NSAID therapy can improve renal perfusion and associated haemodynamic effects such as hypertension
3. The safest option for Ms WR is to manage the pain with regular use of a paracetamol-based product and to withdraw the NSAID thus removing the risk of peptic ulcer disease but also removing the potential detrimental effect the NSAID may have on blood pressure since the patient is just above the target for blood pressure control. Weight loss may also help to reduce the burden on her knees and may also have some positive effect on her blood pressure.

   The relative risk of ulcer complications has been compared among groups of NSAIDs with naproxen being of intermediate risk. Different NSAIDs vary in their selectivity for COX isoenzymes and may account for the relative toxicities observed. Selective COX-2 inhibitors are associated with low risk but are contraindicated in patients with

cardiovascular disease as they have been associated with an increased incidence of myocardial infarction. However, some other non-selective NSAIDs have also been associated with thrombotic risk, although naproxen seems to have the lowest risk and so is an appropriate choice of NSAID if indicated in this patient. There is no clear evidence to test for and eradicate *H. pylori* in chronic NSAID users.

An assessment of Ms WR's pain should be undertaken and the risks associated with naproxen use should be explained to the patient who may be willing to change to regular paracetamol with the addition of codeine if necessary. Otherwise adding a standard dose of PPI to naproxen reduces the gastro-intestinal risks but not the renal risks.

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Inflammatory bowel disease 13

S. E. Cripps

Key points

- Ulcerative colitis and Crohn's disease are the two most common inflammatory bowel diseases (IBD) of the gut. Both are chronic relapsing conditions with a high morbidity and remain largely incurable.
- Ulcerative colitis and Crohn's disease are similar but there are contrasting features which relate to the site of involvement and extent of inflammation across the bowel wall. Ulcerative colitis is limited to the large bowel and the mucosa, whereas Crohn's disease frequently involves the small intestine with inflammation extending through the bowel wall to the serosal surface.
- The aims of treatment are to control acute attacks promptly and effectively, induce remission, maintain remission and identify patients who will benefit from surgery.
- Choice and route of therapy will depend on site, extent and severity of the disease together with knowledge of current or previous treatment.
- A reduction in inflammation with corticosteroids and aminosalicylates is the mainstay of treatment, with immunosuppressants (e.g. azathioprine, methotrexate, ciclosporin) and biologic agents (e.g. infliximab and adalimumab), reserved for more severe and refractory cases.
- The management of IBD poses a challenge to the multidisciplinary team both clinically and economically.
- National standards for IBD aim to ensure patients receive consistent, high-quality care and IBD services throughout the UK are evidence based, engaged in local and national networking, based on modern IT and meet specific minimum standards.

Introduction

Inflammatory bowel disease (IBD) can be divided into two chronic inflammatory disorders of the gastro-intestinal tract, namely Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease affects any part of the gastro-intestinal tract whereas ulcerative colitis affects the colon and rectum only. Current available treatment for IBD is not curative. IBD follows a relapsing and remitting course that is unpredictable and causes disruption to a patient's lifestyle and places a burden on the workplace and healthcare setting. The management of IBD patients poses a challenge to the multidisciplinary team both clinically and economically.

Epidemiology

The incidence of IBD is greater in North America, Europe, Australia and New Zealand, although the incidence in Africa, Asia and South America is rising steadily. This increase in developing countries may be due to improved sanitation and vaccination programmes along with a decreased exposure to enteric infections. Jewish and Asian people living in USA and UK are more commonly affected by IBD than those living in Israel and Asia. There appears to be no association between IBD and social class. The peak incidence of IBD occurs between 10 and 40 years, although it can occur at any age, with 15% of cases diagnosed in individuals over the age of 60 years. The incidence appears equal between males and females, although some studies in Crohn's disease show a slight female predominance. Up to 240,000 people are affected by IBD in the UK.

The incidence of new cases of ulcerative colitis in Europe and USA is 2–8 per 100,000 per year with a prevalence of 40–80 per 100,000 per year. The incidence has remained fairly static over the last 40 years. In the UK, Crohn's disease occurs with a similar frequency to ulcerative colitis with around 4 per 100,000 per year and a prevalence of 50 per 100,000. The rates in central and southern Europe are lower. In South America, Asia and Africa, Crohn's disease is uncommon but appears to be on the rise (Mpofu and Ireland, 2006).

Aetiology

The causative agents of IBD are largely unknown, although a number of factors are thought to play a role.

Environmental

Diet

Evidence that dietary intake is involved in the aetiology of IBD is inconclusive, although several dietary factors have been associated with IBD, including fat intake, fast food ingestion, milk and fibre consumption, and total protein and energy intake. A large number of case-control studies have reported a causal link between the intake of refined carbohydrates and Crohn's disease (Gibson and Shepherd, 2005). The mechanism for diet as a trigger is very poorly understood.

During the course of the disease, patients are able to identify foods which aggravate or exacerbate their symptoms, for example, milk or spicy foods. Up to 5% of patients with ulcerative colitis improve by avoiding cow's milk, whilst patients with Crohn's disease improve if they start to take elemental (amino acid based), oligomeric (peptides) and polymeric (whole protein) feeds, although symptoms may return when their normal diet is reintroduced.

Those that are breastfed as infants have a reduced risk of developing IBD (Mpofu and Ireland, 2006).

Smoking

There is a higher rate of smoking amongst patients with Crohn's disease than in the general population, with up to 40% of patients with the disease being smokers. Smoking worsens the clinical course of the disease and increases the risk of relapse and the need for surgery. Fewer patients with ulcerative colitis smoke (approximately 10%). Former smokers are at the highest risk of developing ulcerative colitis, while current smokers have the least risk. Stopping smoking can provoke the emergence of ulcerative colitis. This indicates that smoking may help to prevent the onset of the disease. The explanation for this is unclear. However, it is thought that in addition to its effect on the inflammatory response, the chemicals absorbed from cigarette smoke affect the smooth muscle inside the colon, potentially altering gut motility and transit time. In some studies, nicotine has been shown to be an effective treatment for ulcerative colitis (Guslandi, 1999).

Infection

Exposure to *Mycobacterium paratuberculosis* has been considered a causative agent of Crohn's disease, although current evidence indicates it is not an aetiological factor.

Ulcerative colitis may present after an episode of infective diarrhoea, but overall there is little evidence to support the role of a single infective agent.

Enteric microflora

Enteric microflora plays an important role in the pathogenesis of IBD because the gut acts as a sensitising organ that contributes to the systemic immune response. Patients with IBD show a loss of immunological tolerance to intestinal microflora and consequently antibiotics often play a role in the treatment of IBD. More recently, manipulating the intestinal flora using probiotics, prebiotics and symbiotic has proven to be an effective therapeutic strategy. Probiotics such as *Bifidobacteria* and *Lactobacilli* alter the intestinal microflora balance favourably. Prebiotics stimulate the growth of specific, beneficial microorganisms in the colon whilst synbiotics, a combination of both prebiotics and probiotics, have been successfully used.

Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac have been reported to exacerbate IBD (Felder et al., 2000). It is thought this may result from direct inhibition of the synthesis of cytoprotective prostaglandins. Antibiotics may also precipitate a relapse in disease due to a change in the enteric microflora. The risk of developing Crohn's disease is thought to be increased in women taking the oral contraceptive pill, possibly caused by vascular changes.

MMR vaccine. There has been much debate about the link between bowel disease and measles, measles vaccine or combined measles, mumps and rubella (MMR) immunisation. However, current evidence has indicated no proven correlation.

Appendicectomy

Appendicectomy has a protective effect in both Crohn's disease and ulcerative colitis (Radford-Smith et al., 2002). It is unclear whether this protective effect is immunologically based or whether individuals who develop appendicitis and consequently have an appendicectomy are physiologically, genetically or immunologically distinct from the population that is predisposed to IBD.

Stress

Some patients find that stress triggers a relapse in their IBD and this has been reproduced in animal models. It is thought that stress activates inflammatory mediators at enteric nerve endings in the gut wall. In addition to stress as a trigger factor, living with IBD can also be stressful. Its chronic nature, lack of curative treatment, distressing symptoms and impact on lifestyle make it difficult for patients to cope.

Genetic

Fifteen percent of first degree relatives have IBD. There is mounting evidence that Crohn's disease and ulcerative colitis result from an inappropriate response of the immune system in the mucosa of the gastro-intestinal tract to normal enteric flora (Ahmad et al., 2004). Since the mid-1990s there has been considerable progress in understanding the contribution of genetics to IBD susceptibility and phenotype.

Mutations of the gene CARD15/NOD2 located on chromosome 16 have been associated with small intestinal Crohn's disease in white but not oriental populations. Two other genes have been recently linked with Crohn's disease (OCTN1 on chromosome 5 and DLG5 on chromosome 10).

Genetic studies in ulcerative colitis have shown human lymphocyte antibody (HLA) is more strongly linked. Genotype related to pattern of disease (HLA-DRI*103) is 5–11 times more common in patients who have undergone colectomy.

Ethnic and familial

Jews are more prone to IBD than non-Jews, with Ashkenazi Jews having a higher risk than Sephardic Jews. In North America, IBD is more common in whites than blacks. First-degree relatives of those with IBD have a 10-fold increase in

risk of developing the disease. A familial link is supported from research showing a 15-fold greater concordance for IBD in monozygotic (identical) than dizygotic (non-identical) twins (Jess et al., 2005).

Pathophysiology

In individuals with IBD, trigger factors typically cause a severe, prolonged and inappropriate inflammatory response in the gastro-intestinal tract and the ongoing inflammatory reaction leads to an alteration in the normal architecture of the digestive tract. Genetically susceptible individuals seem unable to downregulate immune or antigen non-specific inflammatory responses. It is thought that chronic inflammation is characterised by increased activity of effector lymphocytes and pro-inflammatory cytokines that override normal control mechanisms. Others, however, have suggested that IBD may result from a primary failure of regulatory lymphocytes and cytokines, such as interleukin-10 and transforming growth factor-β, to control inflammation and effector pathways. In Crohn's disease, it is also thought that T-cells are resistant to apoptosis after inactivation. Non-pathogenic bowel flora appears to be an essential factor.

Disease location

The character and distribution, both macroscopic and microscopic, of chronic inflammation define and distinguish ulcerative colitis and Crohn's disease. Table 13.1 shows the differences in location and distribution of ulcerative colitis and Crohn's disease. Figure 13.1 details the histological differences.

Crohn's disease

Crohn's disease can affect any part of the gut from the mouth to the anus. Approximately 45% of patients have ileocaecal disease, 25% colitis only, 20% terminal ileal disease, 5% small

Table 13.1 Location and distribution of ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Location	Colon and rectum 40% proctitis 20% pancolitis 10–15% backwash ileitis	Entire gut (mouth to anus, rectal sparing) 45% ileocaecal disease 25% colitis only 20% terminal ileal disease 5% small bowel disease 5% anorectal, gastroduodenal, oral disease
Distribution	Continuous, diffuse No granulomas Inflammation of mucosa Ulceration if fine and superficial	Often discontinuous and segmental 'skip lesions' Full thickness (transmural) Granulomatous inflammation Deep ulceration with mucosal extension
Fissures, fistulae and stricture	Absent	Common
Perianal disease	Absent	Present

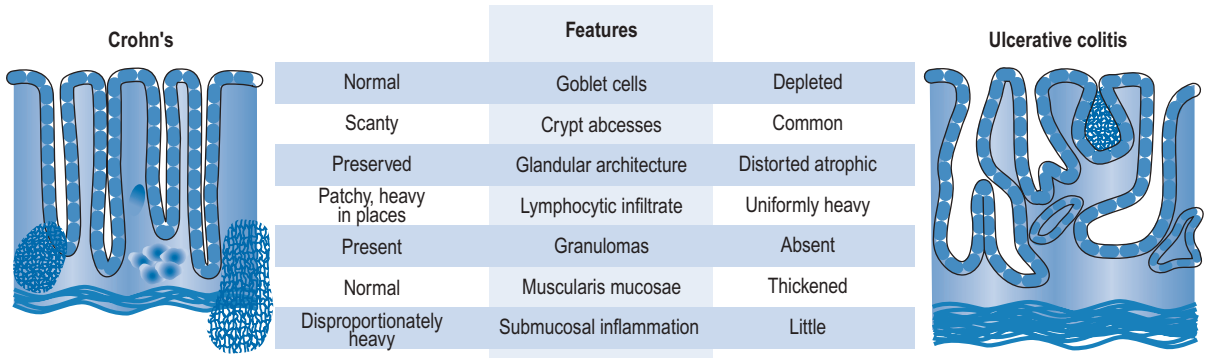

Fig. 13.1 Histological features in the rectal biopsy that help to distinguish between ulcerative colitis and Crohn's disease (from Misiewicz et al., 1994, with kind permission from Blackwell Scientific Publications, Oxford).

bowel disease and 5% anorectal, gastroduodenal or oral disease. Crohn's disease can involve one area of the gut or multiple areas, with unaffected areas in between being known as 'skip lesions'. The areas of the small bowel affected are typically thickened and narrow. A 'red ring' is often the first visible abnormality seen on colonoscopy. This is a lymphoid follicular enlargement with a surrounding ring of erythema, which develops into aphthoid ulceration and may progress to deep fissuring ulcers with a cobblestone appearance, fibrosis and strictures. Intestinal strictures arise from chronic and extensive inflammation and fibrosis and bowel obstruction may arise. Local gut perforation may cause abscesses which may also lead to fistulae.

Microscopically, inflammation extends through all layers of the bowel. Inflammatory cells are seen throughout, resulting in ulceration and microabscess formation. Non-caseating epithelioid cells, sometimes with Langhans' giant cells, are seen in about 25% of colonic biopsies and in 60% of surgically resected bowel. Chronic inflammation in the small intestine, colon, rectum and anus leads to an increased risk of carcinoma.

Ulcerative colitis

At first presentation, ulcerative colitis is confined to the rectum (proctitis) in 40% of cases, the sigmoid and descending colon (left-sided colitis) in 40% and the whole colon (total ulcerative colitis or pancolitis) in 20% of cases. Proctitis extends to involve more of the colon in a minority, with 15–30% of patients developing more extensive disease over 10 years. The reason why some patients have extensive disease and some have limited disease is unknown. In severe total ulcerative colitis, there may also be inflammation of the terminal ileum. This is known as 'backwash ileitis' but is not clinically significant. The colon appears mucopurulent, erythematous and granular with superficial ulceration that in severe cases leads to ulceration. As the colon heals by granulation, post-inflammatory polyps may form.

Microscopically, superficial inflammation is seen with inflammatory cells infiltrating the lamina propria and crypts. Crypt abscesses occur, the crypt structure is lost and goblet cell depletion arises as mucin is lost. Dysplasia, which can potentially progress to carcinoma, may be seen in biopsies taken from patients with long-standing total colitis.

Other types of colitis

Crohn's disease yet to be classified (sometimes referred to indeterminate colitis) is when chronic colitis persists, yet the pathology of the disease has not been identified as either Crohn's disease or ulcerative colitis. In microscopic colitis, the main feature is watery diarrhoea in the presence of a normal colonoscopy and chronic inflammation in the absence of crypt architectural distortion on mucosal biopsies. Drugs such as NSAIDs and proton pump inhibitors (PPIs) are implicated as the cause in up to 50% of cases of microscopic colitis. Diversion colitis is when inflammation occurs in the defunctioned loop of a colostomy causing a mucous discharge. Pseudomembraneous colitis is caused by *Clostridium difficile*, usually after prolonged or multiple antibiotics. The use of PPIs predisposes patients to infection. It is diagnosed by sigmoidoscopy and detection of *C. difficile* toxin in the stool.

Clinical manifestation

The clinical differences between Crohn's disease and ulcerative colitis are described in Table 13.2.

Crohn's disease

The clinical features of Crohn's disease depend largely on the site of the bowel affected, the extent, severity and the pathological process in each patient. Crohn's disease tends to be more disabling than ulcerative colitis with 25% of patients unable to work 1 year after diagnosis. The predominant symptoms in Crohn's disease are diarrhoea, abdominal pain and weight loss. Weight loss occurs in most patients, irrespective of disease location. Ten to twenty percent of patients will have weight loss greater than 20%. The main cause is decreased oral intake, although malnutrition is also common. There is a slight increase in mortality in patients with extensive Crohn's disease.

Small bowel, ileocaecal and terminal ileal disease

Patients present with pain and/or a tender palpable mass in the right iliac fossa with weight loss and diarrhoea, which usually contains no blood. Diarrhoea is caused by mucosal inflammation, bile salt malabsorption that causes steatorrhoea or bacterial growth proximal to a stricture. Small bowel obstruction may also occur as a consequence of inflammation, fibrosis and stricture formation. Patients often describe a more generalised intermittent pain which is colicky with loud gurgling bowel sounds (borborygmi), abdominal distension, vomiting and constipation. When inflammation or abscesses are the predominant pathology, many patients present with constant pain and fever. Enteric fistulae occur and may involve the skin, bladder or vagina. Although rare, perforation of the gut may present with an acute abdomen and peritonitis. Vitamin B_{12} and folic acid deficiencies predispose patients with disease of the terminal ileum to macrocytic anaemia, while bile acid malabsorption also occurs in such patients and predisposes them to cholesterol gallstones and oxalate renal stones.

Colitis

The main symptoms are abdominal pain, profuse and frequent diarrhoea (more than six loose stools per day) with or without blood, and weight loss. Patients also complain of lassitude, anorexia and nausea and appear thin, tachycardic, anaemic, malnourished and febrile. Colitis may present

Table 13.2 Clinical differences between ulcerative colitis and Crohn's disease

Symptom	Ulcerative colitis	Crohn's disease
Prominent symptom	Bloody diarrhoea	Diarrhoea, abdominal pain, weight loss 30%, no gross bleeding
Fever	++	++
Abdominal pain	Variable	++
Diarrhoea	+++	+++
Rectal bleeding	+++	++
Weight loss	+	++
Sign of malnutrition	+	++
Abdominal mass	–	++
Dehydration	+++	++
Iron-deficiency anaemia, raised CPR/ESR, hypoalbuminaemia	++	++

CPR, C-reactive protein; ESR, erythrocyte sedimentation rate; +, the likelihood this symptom will be present; –, symptom absent in patient.

insidiously with minimal discomfort. Patients with severe involvement of the colon or the terminal ileum often have electrolyte abnormalities, hypoalbuminaemia and iron-deficiency anaemia. Extra-intestinal complications are more common in those patients with large bowel disease.

Perianal disease

Patients may present with an anal fissure, fistula or a perirectal abscess. These symptoms can have a significant impact on the patient's lifestyle.

Gastroduodenal and oral disease

These are both rare conditions. Gastroduodenal Crohn's disease presents as dyspepsia, pain, weight loss, anorexia, nausea and vomiting. Oral disease is very painful and may cause chronic ulceration resulting in anorexia.

Stricturing Crohn's disease

Patients presenting with pain, vomiting and constipation and a diagnosis of stricturing disease can lead to perforation if not surgically treated, although this is rare (see Fig. 13.2)

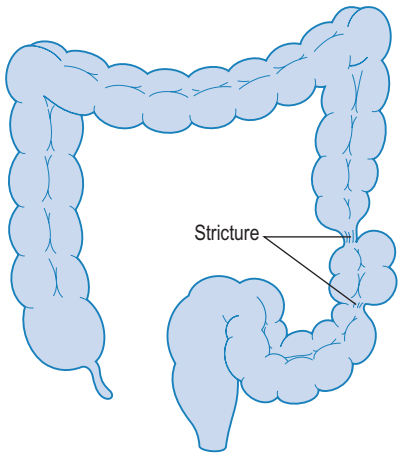

Fig. 13.2 Stricture formation in Crohn's disease.

Ulcerative colitis

Typical symptoms of ulcerative colitis include bloody diarrhoea (the most predominant symptom) with mucus, abdominal pain with fever, and weight loss in severe cases. The typical appearance of a patient diagnosed with Crohn's disease is low BMI, malabsorption, weight loss and growth retardation. Frank blood loss is more common in ulcerative colitis than Crohn's disease. The symptoms of ulcerative colitis are similar to Crohn's colitis with patients being tachycardic, anaemic, febrile, fatigued, dehydrated and thin. Approximately 50% of patients with ulcerative colitis have some form of relapse each year, and severe attacks can be life-threatening. Up until the 1960s, one-third of ulcerative colitis patients died from the condition; with advances in medical and surgical treatment death is now extremely rare.

Acute severe disease

In addition to the typical symptoms of ulcerative colitis, patients with acute severe disease may present with more than six bloody stools per day (10–20 liquid stools per day is not unusual), with a fever (>37.8 °C), tachycardia (>90 bpm), anaemia (Hb < 10.5 g/dL) or elevated inflammatory markers (ESR > 30 mm/h; CRP > 8). Severity is commonly assessed using the Truelove and Witts criteria (see investigations).

Moderately active disease

Stool frequency is less than six motions each day with diarrhoea, mucus and rectal bleeding. Moderatively active disease is more common in 'left-sided' disease. Toxic megacolon is rare in patients with rectosigmoidal involvement, and the incidence of colon cancer is much lower in these patients than those with total colitis.

Proctitis

The manifestations of active proctitis are less severe. These are tenesmus, pruritus ani, rectal bleeding and mucous discharge. Patients are often constipated.

Toxic dilatation

This can occur in untreated severe ulcerative colitis. There is a high risk of perforation with a mortality of 50%.

Extra-intestinal complications of IBD

Around 20–30% of patients with IBD will present with extra-intestinal manifestations. They are more commonly seen in patients where IBD affects the colon. Complications affect the joints, skin, bone, eyes, liver and biliary tree and are more common in active disease. Figure 13.3 highlights some of the extra-intestinal features of IBD.

Joints and bones

Arthropathies occur in 10% of patients with IBD, are more common in women and are a well-recognised complication of IBD. Patients with pauciarticular disease, characterised by arthritis limited to five or fewer joints, often experience a flare in the arthropathy when there is an exacerbation of the IBD symptoms. When the IBD relapse is treated, the arthropathy improves. In contrast, in polyarticular arthropathy, a chronic condition which affects more than five joints, a flare of the IBD appears not to be temporally related to the activity of the arthropathy. About 5% of patients with IBD also have ankylosing spondylitis. This is thought to be immunologically mediated and not associated with IBD activity. Osteopenia, potentially leading to osteoporosis, is often seen in patients with IBD because of chronic steroid use (particularly when the cumulative dose of prednisolone exceeds 10 g) and/or malabsorption.

Skin

Both erythema nodosum and pyoderma gangrenosum are associated with IBD. Erythema nodosum appears as tender, hot, red nodules that subside over a few days to leave a brown

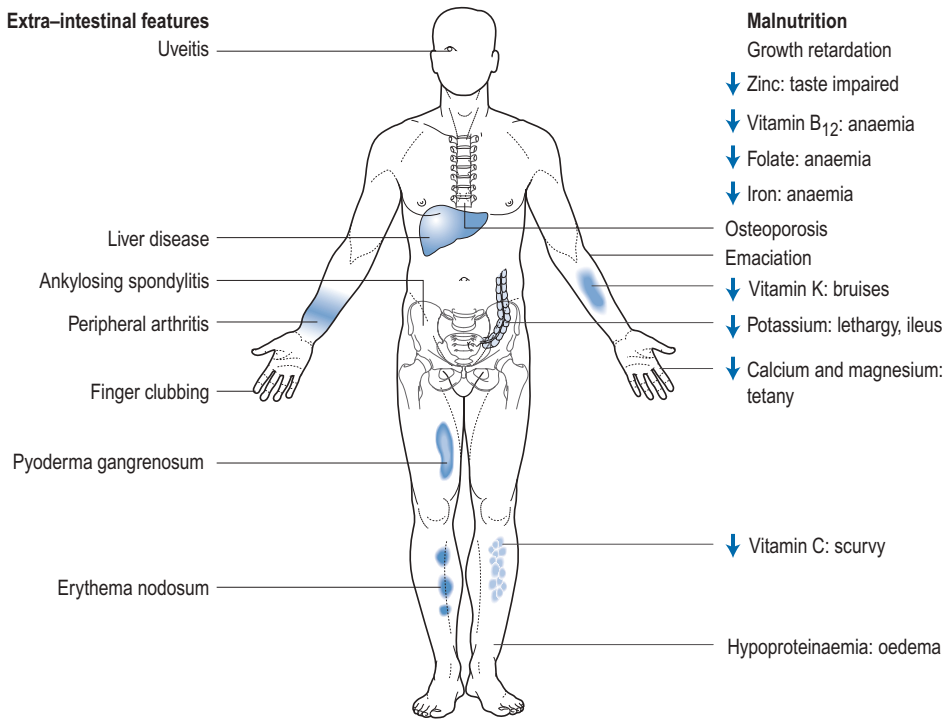

Fig. 13.3 Some of the extra-intestinal illnesses and features of malnutrition found in patients with inflammatory bowel disease (from Misiewicz et al., 1994, with kind permission from Blackwell Scientific Publications, Oxford).

skin discolouration. Disease flares are normally directly related to IBD activity in the 8% of patients affected.

Pyoderma gangrenosum presents as a discrete pustule that develops into an ulcer. In the 2% of patients affected, IBD activity does not appear to be directly related to the pyoderma gangrenosum, which may begin or worsen when the IBD is quiescent.

Sweet's syndrome (an acute febrile neutrophillic dermatosis) which has some similarity to erythema nodosum may also be associated with IBD.

Eye

Ocular complications are infrequent, occurring in less than 10% of cases. Episcleritis (intense burning and itching with localised area of blood vessels) is the most common complication of IBD. Scleritis, which involves more of the eye, may impair vision. Uveitis (headache, burning red eye, blurred vision) is often associated with joint and skin manifestations of IBD. Conjunctivitis is frequently seen in IBD patients but is not specific and no true association has been demonstrated.

Hepatobiliary

Biliary complications of IBD are gallstones and sclerosing cholangitis which occurs in 5% of patients with ulcerative colitis but less frequently in those with Crohn's disease. Conversely the prevalence of IBD (mostly ulcerativ colitis) in patients with sclerosing cholangitis is 70–80%. Sclerosing cholangitis, found predominantly in males, is a chronic cholestatic condition characterised by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. Patients present with obstructive jaundice, cholangitis and raised liver enzymes (alkaline phosphatase and γ-glutamyltranspeptidase). Endoscopic retrograde cholangiopancreatography (ERCP) is useful in diagnosing and aiding the stenting of strictures. There is an increased risk of cholangiocarcinoma, with a liver transplant the only cure. Hepatic complications of IBD include fatty liver, pericholangitis, chronic active hepatitis and cirrhosis.

Thromboembolic

Thromboembolic complications occur in around 1–2% of IBD patients. The most common cause of death in hospitalised IBD patients is pulmonary embolism (Solem et al., 2004).

Anaemia

Around one-third of patients have haemoglobin levels below 12 g/dL. The main causes are chronic intestinal bleeding with iron loss (bowel inflammation) which causes a microcytic anaemia whereas the chronic inflammatory disease can cause normocytic anaemia giving rise to mixed features anaemia. Folate, iron, vitamin B_{12} malabsorption are also common. The side effects of commonly used drugs in IBD, for example, methotrexate and azathioprine can give rise to symptoms of anaemia.

Investigations

Radiological, pathological and clinical investigations help to confirm diagnosis, disease recurrence and response to treatment. Differential diagnoses of IBD include carcinoma, infection, drug-induced colitis, ischaemia, radiation damage, irritable bowel syndrome and diverticulitis.

Endoscopy

The key diagnostic investigation in IBD is lower gastrointestinal tract endoscopy (sigmoidoscopy and colonoscopy), which allows direct visualisation of the large bowel and histopathological assessment from biopsies. The risk of developing colorectal cancer is 7–10% after 20 years in patients with colonic disease. Therefore, routine surveillance colonoscopy is essential in the early detection of colorectal cancer. Treatment response to biologics, for example infliximab, can be assessed via mucosal healing seen at colonoscopy.

In patients with severe symptoms, it is sometimes necessary to delay a full colonoscopy because of the increased risk of perforation. Wireless capsule endoscopy is a relatively new procedure where the small bowel can be viewed and can be useful in patients with non-stricturing Crohn's disease.

Radiology

Radiological imaging is complementary to clinical and endoscopic assessment. It is used in the initial evaluation or diagnosis, preoperative review, to highlight the presence of complications during exacerbations and to evaluate extraintestinal manifestations. Radiological examination still plays a key role in IBD affecting the small bowel, although endoscopy has generally replaced conventional X-ray examinations of the colon.

Computed tomography (CT scan) and magnetic resonance imagery (MRI) are the best radiological methods for locating and defining fistulae and abscesses in active Crohn's disease.

Radiolabelled leucocyte scans that utilise autologous leucocytes labelled with ^{99}technetium-hexamethylenamine oxime may provide further information of disease site and severity.

Laboratory findings

Although not diagnostic, active disease is suggested in patients with raised inflammatory markers that include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in addition to a low haemoglobin and raised platelet count. Vitamin B_{12} may be low in patients with chronic terminal ileal disease. Low red cell folate and serum albumin, magnesium, calcium, zinc and essential fatty acids also indicate chronic inflammation and malabsorption. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) are more likely to be present in Crohn's disease. Serology can be used to exclude infection as a cause of diarrhoea.

Malabsorption, indicated by low serum trace elements, for example, magnesium and zinc, is not seen in ulcerative colitis. Low albumin may indicate relapse in active disease. Patients with sclerosing cholangitis often present with altered liver function tests.

Stool tests

Red and white blood cells can be seen on microscopic examination of fresh stools. Microscopic identification of infective cells such as amoeba may also be visualised. *C. difficile* toxin can be assessed through culture and toxin assay. Stool tests do not diagnose IBD but contribute to excluding alternative diagnoses.

Clinical assessment tools

The Crohn's Disease Activity Index (CDAI) or the Harvey–Bradshaw Index (HBI) is used in most clinical trials to define remission in Crohn's disease. However, in clinical practice the CDAI is rarely used as it needs to be measured prospectively and is complex. The HBI is a simple measure of stool frequency, pain and other clinical features that is increasingly used to document selection for and response to biologic therapy. A CDAI of <150 or an HBI ≤3 suggests patient is in remission (NICE, 2010).

The Truelove and Witts criteria is a useful tool in defining the severity of ulcerative colitis (see Table 13.3). A severe attack is defined as more than six bloody stools a day plus one or more of the following: pulse >90 beats/min, temperature >37.8 °C, haemoglobin <10.5 g/dL or ESR >30 mm/h. In this case, the patient should be admitted to hospital.

Remission in ulcerative colitis is defined as complete resolution of symptoms with a normal bowel pattern (<3 stools/day), no urgency and no visible bleeding. Mucosal healing is confirmed by endoscopy. Steroid-free remission is the goal of therapy.

Table 13.3 Truelove and Witts criteria for assessing severity of ulcerative colitis (Travis et al., 2008)

Feature	Mild	Moderate	Severe
Motions per day	<4	4–6	>6
Rectal bleeding	Little	Moderate	Large amounts
Temperature	Apyrexial	Intermediate	>37.8 °C on 2 of 4 days
Pulse rate	Normal	Intermediate	>90 bpm
Haemoglobin	Normal	Intermediate	<10.5 g/dL
ESR	Normal	Intermediate	>30 mm/h

ESR, erythrocyte sedimentation rate.

Treatment of inflammatory bowel disease

At present there is no cure for IBD since the exact cause of the condition is unknown. A wide range of drugs and nutritional supplements are available to maintain the patient in long periods of remission in both Crohn's disease and ulcerative colitis. However, surgical intervention will eventually become necessary when the patient relapses and fails to respond to drug therapy. Since the majority of people with IBD are diagnosed under the age of 30, effective treatment and avoidance of relapses is of paramount importance in this chronic long-term condition.

Nutritional therapy

Nutritional therapy can be considered as an adjunctive or primary treatment. Although a potential problem for all patients with IBD, patients with Crohn's disease are at particular risk of becoming malnourished and developing a variety of nutritional deficiencies (Fig. 13.3). It is, therefore, important for patients to receive optimal nutrition and dietary manipulation as needed. Low-fibre diets help to reduce clinical symptoms of intestinal obstruction in Crohn's disease (Fernandes-Banares et al., 1999). Functional and structural damage to the small bowel can cause malabsorption problems and occasionally patients may require a low-lactose diet. Patients with poor oral intake and loss of appetite often respond to supplemental enteral feeds. Enteral nutrition in the form of an elemental or polymeric diet can be used as primary therapy and is widely employed in paediatrics (Heuschkel and Walker-Smith, 1999).

Patients who have extensive small bowel resection may experience many nutritional deficiencies because of malabsorption. Iron depletion, hypoproteinaemia, deficiencies in water- and fat-soluble vitamins, trace elements and electrolytes may all occur and must be corrected using a suitable replacement regimen.

Where appropriate, and when enteral nutrition is not indicated or adequate, a total parenteral nutrition (TPN) regimen may be prescribed. Some patients receive concurrent enteral and parenteral feeding.

Drug treatment

The main goals of drug treatment are to treat acute attacks promptly and effectively, induce and maintain remission, limit drug toxicity, modify the pattern of disease, avoid and/or manage complications and select patients who will benefit from surgery. Morbidity and mortality can also be reduced by the prompt use of effective and appropriate drug therapy. The choice of drug and route of administration depends on the site, extent and severity of the disease together with the individual's treatment history. Drug therapy is often required for many years and patient preference, acceptability and possible side effects not only affect choice but will impact on medication adherence. There is a need for therapeutic strategy and consistency in the management of patients with IBD.

Corticosteroids, aminosalicylates and immunosuppressive agents (immunomodulators) such as azathioprine are the mainstays of treatment. Immunomodulators are not licensed for use in IBD but are routinely used.

Modern advances in treatment, such as the use of humanised monoclonal antibody preparations and other biologic agents which modify the affected biochemical inflammatory pathways, now have a significant role in treatment of the disease. These are likely to be the main area of future development.

Other drugs such as antibiotics, for example, metronidazole, are helpful in some cases, while colestyramine, thalidomide, sodium cromoglicate, bismuth and arsenical salts, nicotine, lidocaine, sucralfate, new steroid entities, cytoprotective agents, aloe vera, probiotics and fish oils are rarely used. However, for some patients they provide alternative or supplemental therapy.

The choice of drug treatment is dependent on whether it is prescribed to induce remission or as maintenance therapy. The majority of patients are managed successfully as hospital outpatients or by their primary care doctor. Only severe extensive or fulminant disease requires hospitalisation and the use of parenteral therapy and/or surgical intervention. Oral medication can be given to most patients for maintenance of moderate disease.

The route of administration is a particularly important factor in IBD. In contrast to most other conditions, minimal systemic absorption and maximal intestinal wall drug levels are required with oral therapy. Several delivery strategies have been used to achieve this including the chemical modification of drug molecules, delayed and controlled-release formulations and the use of bioadhesive particles.

Disease confined to the anus, rectum or left side of the colon is more appropriately treated with rectally administered topical preparations where the drug is applied directly to the site of inflammation (Table 13.4).

These topical preparations have reduced systemic absorption and fewer side effects. Choice of formulation depends on the site of inflammation and also consideration of presentation, acceptability, patient preference and cost. Adherence to topical therapy is generally poor and good patient education is required for effective benefit.

Proctitis is best treated with suppositories. Where inflammation affects the rectum and sigmoid colon (up to 15–20 cm), foam enemas are preferred. In more extensive disease extending to the splenic flexure (30–60 cm), liquid enemas are the agents of choice. However, patients often require a combination of different rectal preparations because, for example, over 90% of liquid enemas bypass the rectum and thereby exert no therapeutic benefit at that site. As a consequence, a suppository may also be required to treat rectal inflammation. The propellant action of foam applicators also results in some preparations by-passing the rectal mucosa. Enemas or suppositories should be administered just before bedtime in a supine position as this allows a much longer retention time. Liquid enemas can be warmed and should be inserted while lying in the left lateral position.

An algorithm for drug treatment in IBD is shown in Fig. 13.4.

Table 13.4 Comparison of commercially available preparations for rectal administration in inflammatory bowel disease

Generic name (proprietary name)	Formulation	Site of release
Sulfasalazine (Salazopyrin®)	Suppositories Retention enema	Rectum Transverse, descending colon and rectum
Mesalazine (Pentasa®, Salofalk®)	Retention enema	Transverse, descending colon and rectum
Mesalazine (Asacol®, Salofalk®)	Foam enema	Rectum and rectosigmoid colon
Mesalazine (Asacol©®, Pentasa®, Salofalk®)	Suppositories	Rectum
Prednisolone sodium phosphate (Predsol®)	Retention enema Suppositories	Transverse, descending colon and rectum Rectum
Prednisolone sodium metasulphobenzoate (Predenema®)	Retention enema	Transverse and descending colon
Prednisolone sodium metasulphobenzoate (Predfoam®)	Foam enema	Rectum and rectosigmoid colon
Prednisolone sodium phosphate (Predsol®)	Retention enema	Transverse and descending colon
Hydrocortisone acetate (Colifoam®)	Foam enema	Rectum and rectosigmoid colon
Budesonide (Entocort©®)	Retention enema	Rectum and rectosigmoid colon

Corticosteroids

The glucocorticoid properties of hydrocortisone and prednisolone are the mainstay of treatment in active ulcerative colitis and Crohn's disease. Prednisolone administered orally or rectally is the steroid of choice, although in emergency situations hydrocortisone or methylprednisolone is used when the parenteral route is required. Corticosteroids have direct anti-inflammatory and immunosuppressive actions which rapidly control symptoms. They can be used either alone or in combination, with a suitable mesalazine (5-aminosalicylic acid, 5-ASA) formulation or immunosuppressant, to induce remission.

Oral corticosteroids should not be used for maintenance treatment because of serious long-term side effects, and abrupt withdrawal should be avoided. Patients should be maintained on aminosalicylates or immunosuppressants, as appropriate, or referred for surgery.

Formulations. Oral prednisolone will control mild and moderate IBD and 70% of patients improve after 2–4 weeks of 40 mg/day. This is gradually reduced over the next 4–6 weeks

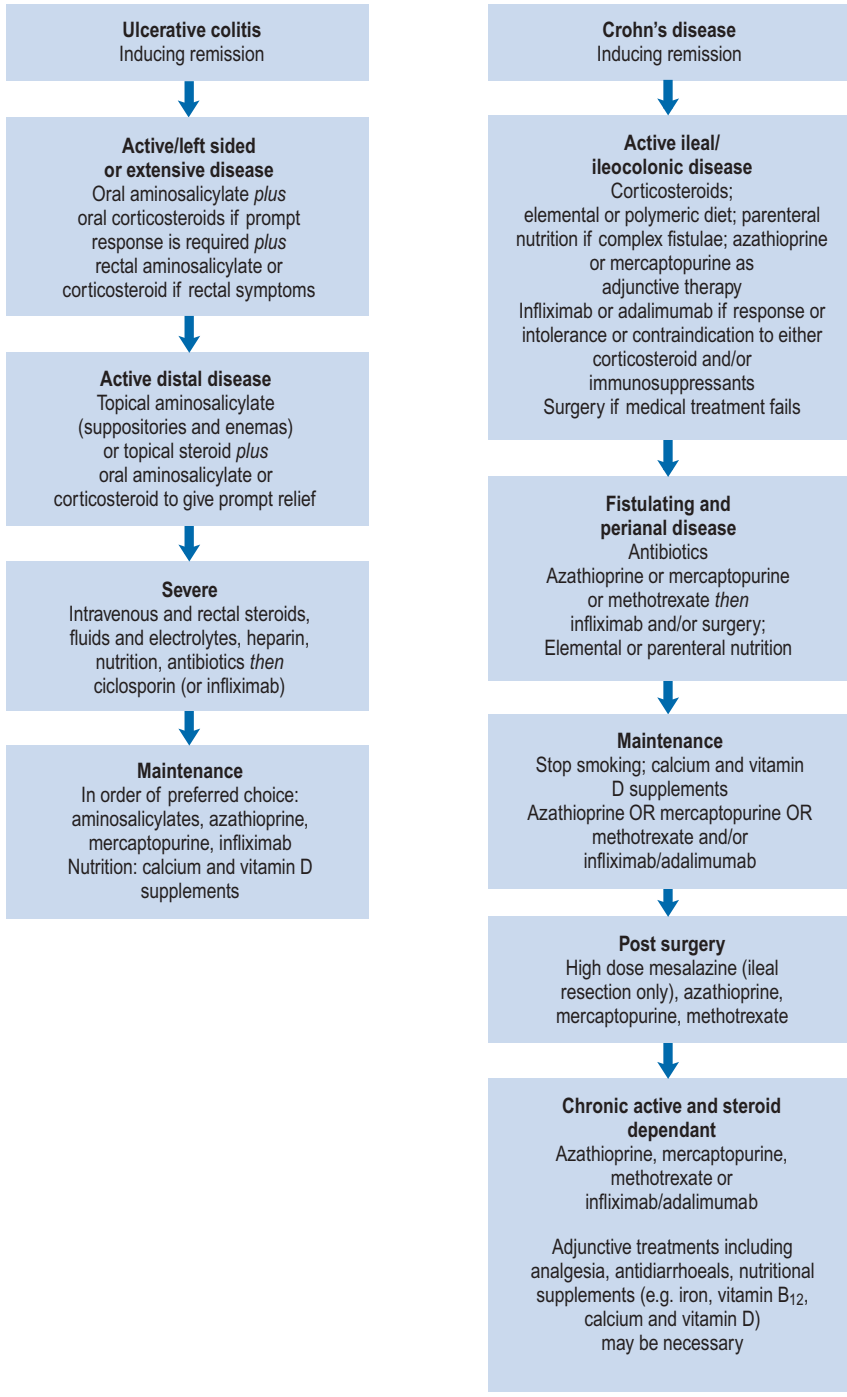

Fig. 13.4 Drug treatment algorithm for inflammatory bowel disease.

to prevent acute adrenal insufficiency and early relapse. An example of a reducing oral prednisolone regime is detailed in Box 13.1.

Oral corticosteroids should be taken in the morning to mimic the diurnal rhythm of the body's cortisol secretion and prevent sleep disturbance. Uncoated steroid tablets are suitable for most patients while enteric-coated preparations do not offer any proven advantage and should be avoided in patients with short bowel or strictures because of poor absorption and bolus release at stricture sites.

Box 13.1 An example of a reducing regimen for oral steroids

40 mg/day for 1 week
30 mg/day for 1 week
20 mg/day for 4 weeks
15 mg/day for 1 week
10 mg/day for 1 week
5 mg/day for 1 week then stop

Local regimen used at the Oxford Radcliffe Hospitals NHS Trust

Severe extensive or fulminant disease requires hospitalisation. Patients are given either hydrocortisone sodium succinate, administered intramuscularly or intravenously at doses of 100 mg three or four times a day, or methylprednisolone 15–20 mg three or four times a day, for 5 days. No additional benefit is gained after 7–10 days. Additional therapy used in severe disease may include intravenous fluid and electrolyte replacement, blood transfusion, topical therapy for rectal and/or colonic involvement, prophylactic heparin (IBD is associated with increased coagulopathy), antibiotics and nutritional support, including possible parenteral nutrition. Oral prednisolone therapy is normally introduced as soon as possible and withdrawn over the following 6–8 weeks. Too rapid reduction is associated with relapse.

Prednisolone at doses higher than 40 mg/day increases the incidence of adverse effects and has little therapeutic advantage. Short-term side effects include moon face, acne, sleep and mood disturbance, dyspepsia, hypokalamia, hypernatraemia and glucose intolerance. Prolonged use can cause cataracts, osteoporosis and increased risk of infection. Doses below 20 mg are not generally effective in active disease (St Clair Jones, 2006). A typical treatment algorithm for the management of an acute attack of IBD is presented in Fig. 13.5.

Rectal corticosteroid preparations are available as suppositories, foam and liquid enemas. In the acute setting, some hospitals make up their own liquid enemas using 100 mg hydrocortisone sodium succinate injection in 100 mL sodium chloride 0.9%. This unlicensed preparation is administered via a burette and soft catheter over 30 min. It is often well tolerated and gives better therapeutic results compared with commercial preparations.

The distribution and absorption characteristics of rectally administered steroids vary greatly. Hydrocortisone (e.g. Colifoam®) is readily absorbed from the rectal mucosa with high peak concentrations compared to prednisolone sodium metasulphobenzoate (e.g. Predenema®) and, to a lesser extent, Predfoam®. Topical preparations may play a role either alone or in combination with oral steroids.

Other steroids

Budesonide, available orally and rectally, is currently licensed for Crohn's disease affecting the ileum and descending colon. It is less effective than conventional corticosteroids in inducing remission in active Crohn's disease, but has fewer side effects than prednisolone because of its rapid and extensive first-pass metabolism. However, the absorbed drug has a higher affinity for glucocorticoid receptors 50–100 times that of prednisolone and so long-term treatment is not advocated. Budesonide has shown to be of benefit in microscopic colitis (Travis et al., 2005). Budesonide enemas are effective in inducing remission in distal ulcerative colitis and are comparable to conventional steroids but probably less effective than mesalazine enemas (Marshall and Irvine, 1997).

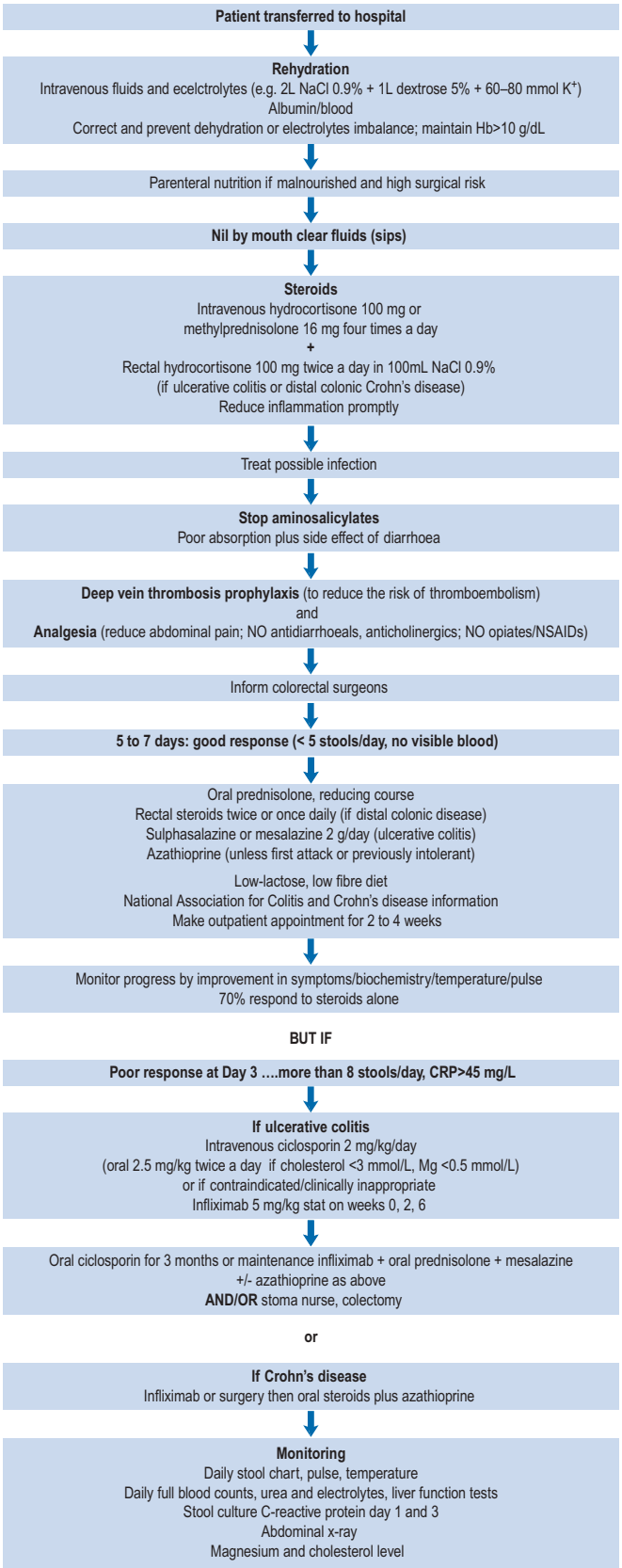

Fig. 13.5 Treatment algorithm for a severe attack of inflammatory bowel disease.

Aminosalicylates

The aminosalicylates currently licensed for the treatment of IBD include sulphasalazine, mesalazine, olsalazine and balsalazide. Their mode of action is unclear but a local effect on epithelial cells by a variety of mechanisms to moderate the release of lipid mediators, cytokines and reactive oxygen species is proposed. Different formulations deliver variable amounts of the active component, mesalazine (5-ASA), to the gut lumen where it exerts a predominantly local action independent of blood levels. The dissolution profile and site of ulceration determine the effectiveness of different preparations.

Diagnosis, disease location, activity, side effect profile, efficacy and cost all affect the choice of aminosalicylate. Available as oral or rectal preparations, aminosalicylates can be used in combination with steroids to induce and maintain remission, in mild to moderate ulcerative colitis. Sulfasalazine is considerably cheaper but the newer aminosalicylates are generally used (Sutherland and MacDonald, 2006). Aminosalicylate maintenance therapy with doses of 1.2 g and above appears to reduce the risk of colorectal cancer by up to 75% (Van Staa et al., 2005).

The use of aminosalicylates in Crohn's disease is less well established (Dignass et al., 2010). There is evidence of patient benefit with high-dose mesalazine (over 2 g/day) in reducing relapse post-small bowel resection.

Sulfasalazine consists of sulfapyridine diazotised to mesalazine. It is broken down by bacterial azoreductase in the colon to mesalazine and sulfapyridine. Sulfapyridine is absorbed in the colon, metabolised by hepatic acetylation or hydroxylation followed by glucuronidation and excreted in urine. Mesalazine is partly absorbed, metabolised by the liver and excreted via the kidneys as *n*-acetyl 5-ASA. However, the majority is acetylated as it passes through the intestinal mucosa. Sulfasalazine itself is poorly absorbed and that which is absorbed is recycled back into the gut, via the bile, either unchanged or as the *n*-acetyl metabolite.

Elimination of sulfapyridine depends on the patient's acetylator phenotype. Those who inherit the 'slow' acetylator phenotype experience more side effects. The dissolution profile of the drug and the site of ulceration determine effectiveness (Fig. 13.6). The optimal dose of sulfasalazine to achieve and maintain remission is usually in the range of 2–4 g per day in 2–4 divided doses. Acute attacks require 4–8 g per day in divided doses until remission occurs, but at these doses associated side effects are often observed.

About 30% of patients taking sulfasalazine experience adverse effects which are either dose related and dependent on acetylate phenotype or idiosyncratic and not dose related. Dose-related side effects include nausea, vomiting, abdominal pain, diarrhoea, headache, metallic taste, haemolytic anaemia, reticulocytosis and methaemoglobinaemia. Side effects which are not dose related include rashes, aplastic anaemia, agranulocytosis, pancreatitis, hepatic and pulmonary dysfunction, renal impairment, peripheral neuropathy and oligospermia. In 3% of patients, acute intolerance may be seen. This often resembles colitis and includes bloody diarrhoea. Adverse effects usually occur during the first 2 weeks of therapy, the majority being related to plasma sulfapyridine levels. Sulfasalazine metabolites are responsible for the yellow colouration of bodily fluids and staining of soft contact lenses.

Mesalazine is tolerated by 80% of patients who are intolerant of sulphasalazine. Many of the sulphonamide-related adverse

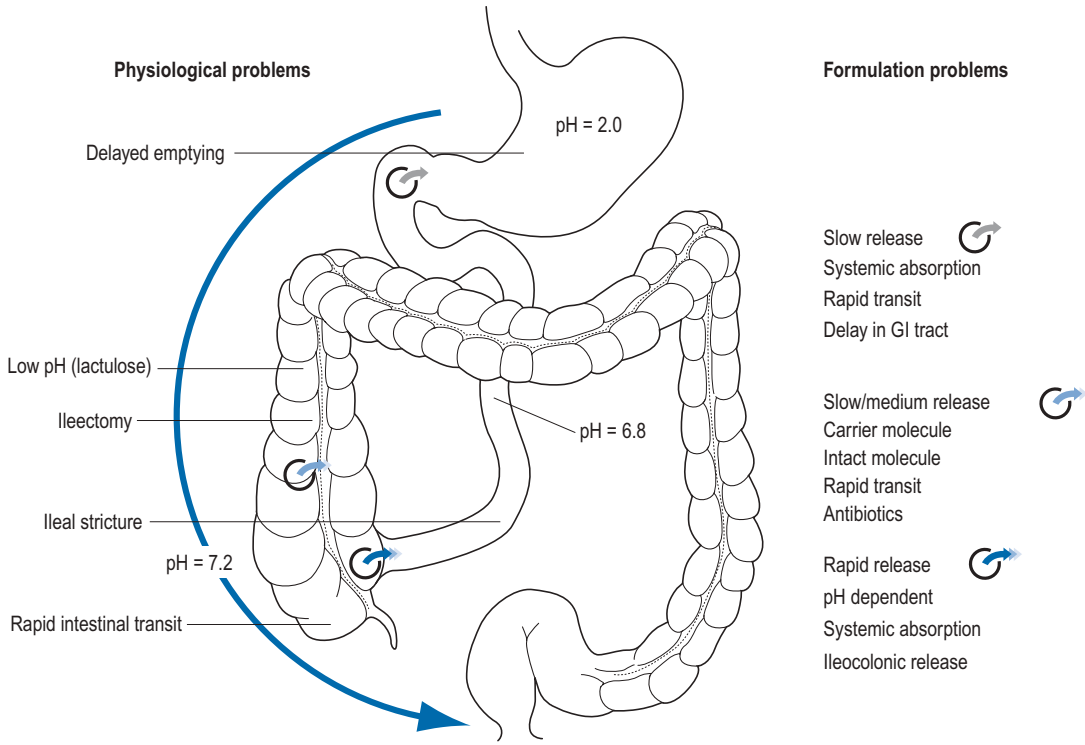

Fig. 13.6 Physiological and formulation problems encountered with mesalazine and delivery systems.

effects of sulfasalazine are avoided by using one of the newer aminosalicylate formulations. However, mesalazine alone can still cause side effects, including blood disorders, pancreatitis, renal dysfunction and lupoid phenomenon. Patients should be counselled on how to recognise and report blood dyscrasias and if they occur, treatment should be stopped.

Formulations. Mesalazine is unstable in acid medium and rapidly absorbed from the gastro-intestinal tract. To increase stability and/or alter the site of release, 5-ASA is modified by different delivery systems (see Fig. 13.6). Mesalazine dose is more important than the delivery system and the lowest systemic absorption preparation should be used. The different delivery systems developed are:

- acrylic resin-coated mesalazine tablet that releases drug pH-dependently;
- ethyl cellulose-coated mesalazine granules that release drug in a time controlled manner;
- diazotisation of mesalazine to itself or to an inert carrier.

All mesalazine preparations are licensed for UC, however only Mesren® MR and Asacol® MR are licensed for Crohn's disease. There are six modified release oral preparations currently licensed in the UK. Asacol® MR, Ipacol®, Mesren® MR and Mezavant® XL contain mesalazine coated with an acrylic resin, Eudragit-S. Mesren® MR and Ipacol® are generic versions of Asacol® MR. Mezavant® XL, recently licensed, is a modified release mesalazine formulation with a patented multi-matrix release system allowing less frequent dosing which may be beneficial in patients experiencing difficulty with a high tablet burden. Salofalk® contains mesalazine coated with Eudragit-L. All these preparations provide pH-dependant release of mesalazine at the mid to terminal ileum and the colon, at pH 7 (Asacol® MR, Mesren® MR, Mezavant® XL) and pH 6 (Ipacol®, Salofalk®). As dissolution occurs at a lower pH with Ipacol® and Salofalk®, this results in a lower ileocolonic mucosal concentration of mesalazine compared with the other pH-dependant release products. There is little clinical difference between the available pH-dependant products Asacol® MR, Mesren® MR and Mezavant® XL. However, cost may contribute to initiating new patients with the cheaper generic. Pentasa® tablets and granules comprise ethyl cellulose-coated granules of mesalazine which are released in the stomach. Mesalazine is leached slowly and continuously from the granules throughout the gastro-intestinal tract at all physiological pH.

It is very important to maintain patients on the same brand of mesalazine as some may relapse because of the different release profiles of the active drug. Therefore, mesalazine should always be prescribed by brand.

Evidence suggests that there is no difference in splitting the dose of mesalazine products as licensed, compared to taking the total dose once daily.

Dipentum® 250 mg capsules and 500 mg tablets contain olsalazine sodium, a dimer of mesalazine. Like sulfasalazine, it remains intact until it reaches the colon where it undergoes bacterial cleavage, releasing two molecules of mesalazine. Olsalazine-induced diarrhoea may help patients with distal disease and proximal constipation. Colazide® 750 mg capsules contain balsalazide sodium, a pro-drug of mesalazine, which relies on bacterial cleavage in the colon, releasing mesalazine from 4-aminobenzoyl β-alanine, the inert carrier molecule.

Table 13.5 Comparison of available oral aminosalicylate preparations for patients with IBD

Generic (proprietary) name	Formulation	Release profile	Site of release
Sulfasalazine (Salazopyrin®)	Compressed tablet, plain and film coated	Azo-linked, independent of pH	Terminal ileum and colon
Mesalazine (Asacol®)	Compressed tablet, acrylic coating	Acrylic coating dissolving at pH 7	Terminal ileum and colon
Mesalazine (Mesren®)	Compressed tablet, acrylic coating	Acrylic coating dissolving at pH 7	Terminal ileum and colon
Mesalazine (Salofalk®)	Compressed tablet and/or capsule, acrylic coating	Acrylic coating dissolving at pH 6	Terminal ileum and colon
Mesalazine (Mezavant® XL)	Compressed tablet, acrylic coating	Multi-matrix release system	Terminal ileum and colon
Mesalazine (Ipacol®)	Compressed tablet and/or capsule, acrylic coating	Acrylic coating dissolving at pH 6	Mid-jejunum ileum and colon
Mesalazine (Pentasa®)	Microgranules coated with ethyl cellulose and compressed into tablets. Granules also available	Disintegration not dependent on pH. Slow dissolution rate	Stomach, duodenum, jejunum, ileum and colon
Olsalazine (Dipentum®)	Hard gelatin capsules and tablets, uncoated	Azo-linked disintegration independent of pH	Terminal ileum and colon
Balsalazide (Colazide)	Hard gelatin capsules	Azo-linked disintegration independent of pH	Terminal ileum and colon

Table 13.5 compares the oral aminosalicylate preparations currently available.

Mesalazine enemas (1 g in 100 mL), foam enemas (1 g per application) or suppositories (250 mg, 500 mg and 1 g) are effective alternatives for treating distal ulcerative colitis and proctitis. The optimum rectal dose is 1 g. Rectal administrations of 5-ASA formulations are significantly better than rectal corticosteroids in inducing remission in ulcerative colitis but steroids are considerably cheaper (Travis et al., 2008). In severe ulcerative colitis, oral and topical formulations should be combined to give prompt symptom relief. Topical and oral 5-ASA is better than either alone (Marteau et al., 2005).

Immunosuppressants

Azathioprine, 6-mercaptopurine, methotrexate, ciclosporin and mycophenolate are immunosuppressants used in patients unresponsive to steroids and aminosalicylates or who relapse when steroids are withdrawn. They are used to induce and maintain remission. All are unlicensed for use in IBD but are routinely used. Treatment may be for up to 5 years because earlier withdrawal increases the rate of relapse. They can take several weeks to work and require regular monitoring.

Thioguanines (azathioprine, mercaptopurine). Azathioprine is metabolised to 6-mercaptopurine by the liver. Both azathioprine and 6-mercaptopurine have steroid-sparing properties. Although the action in IBD is unclear, their active metabolites inhibit purine ribonucleotide synthesis which may in turn inhibit lymphocyte function, primarily T-cells. Mercaptopurine is further metabolised to 6-thioguanine nucleotides.

The main indications for thioguanines are when patients

- require two or more steroid courses in 1 year;
- have chronic active disease unresponsive to steroids or 5-ASAs;
- relapse when steroids are withdrawn (within 3 months) or when the dose is reduced below 15 mg;
- require post-operative prophylaxis of complex Crohn's disease (fistulising or extensive disease).

Oral maintenance doses for azathioprine are usually 2–2.5 mg/kg/day and for mercaptopurine, 1–1.5 mg/kg/day. Doses are adjusted to patient response, tolerance, white cell and platelet counts. Patients are usually prescribed a reducing dose of corticosteroid in addition because mercaptopurine and azathioprine can take several weeks to show a therapeutic benefit.

Seventy percent of patients will tolerate azathioprine. Of the remaining 30%, most will tolerate mercaptopurine. The most common side effects occur within 2–3 weeks of starting treatment and rapidly stop on withdrawal. These include flu-like symptoms (myalgia, headache), nausea and diarrhoea. Nausea is reduced by taking the medicine with food. Although rare (<3%), leucopenia can develop suddenly and unpredictably. Hepatotoxicity and pancreatitis have also been reported in less than 5% of patients. Thioguanine has been used but is associated with a greater risk of hepatotoxicity. There is no evidence that the incidence of lymphoma increases with the use of these agents (St Clair Jones, 2006).

The value of assessing thiopurine methyl transferase (TPMT) activity and genotype, especially prior to initiating treatment, is debatable. Patients who develop leucopenia and are TPMT deficient have a greater risk of myelotoxicity. However, this may not apply in IBD. Some gastroenterologists measure TPMT if a patient has relapsed on doses greater than 2 mg/kg/day to identify fast metabolisers who may respond to higher doses. Measuring TPMT activity to identify the 0.3% of non-metabolisers who are at high risk of rapid leucopenia has also been recommended (Carter et al., 2004).

One of the most significant drug interactions is with allopurinol which inhibits the principal pathway for detoxification of azathioprine and mercaptopurine. Patients receiving these drugs concomitantly should have their dose of azathioprine reduced to approximately one-third to a quarter of the usual dose.

Methotrexate. A low-dose regimen of methotrexate is effective in inducing and maintaining remission in patients with chronically active Crohn's disease. Patients receive once-weekly doses of methotrexate ranging from 15 to 25 mg on the same day each week. These can be given orally or by subcutaneous or intramuscular injection. Oral medication is more practical, although parenteral administration may be more effective and better tolerated. Methotrexate is reserved for patients intolerant or unresponsive to thioguanines.

Methotrexate metabolites inhibit dihydrofolate reductase, although this cytotoxic action does not explain the drug's anti-inflammatory effect. Inhibition of cytokine and eicosanoid synthesis and modification of adenosine levels probably contribute.

Adverse effects associated with methotrexate are essentially gastro-intestinal (nausea, vomiting, diarrhoea and stomatitis). These may also be reduced by prescribing weekly doses of folic acid 5 mg. Folic acid should not be taken on the same day as the methotrexate. Monitoring is undertaken because of the serious side effects of hepatotoxicity, bone marrow suppression and pneumonitis.

Methotrexate is teratogenic and all male and female patients should be counselled about using contraception while taking the medication and also for 3 months after therapy is withdrawn. Guidance to improve the safety of methotrexate use and minimise the potential risk of overdose has been issued (NPSA, 2006). Measures include the issue of patient hand-held monitoring cards detailing dose and blood test results, comprehensive written and verbal medicines information, dispensing one strength of tablet (2.5 mg) and ensuring inpatient medication charts clearly state once-weekly dosing and the number and strength of tablets routinely used. An aide memoire commonly recommended to patients to remember dose frequency is to take methotrexate on Mondays and folic acid on Fridays.

Ciclosporin. Ciclosporin is a calcineurin inhibitor that acts at an early stage on precursors of helper T-cells by interfering with the release of interleukin-2. This inhibits the formation of the cytotoxic lymphocytes which cause tissue damage. Both controlled and uncontrolled studies suggest that ciclosporin is

effective rescue therapy for severe ulcerative colitis failing to respond to intravenous steroids (Campbell et al., 2005). Its use in Crohn's disease is unproven.

The effectiveness of ciclosporin at doses of 2–5 mg/kg/day in treating IBD has been studied in patients refractory to conventional drug therapy (Van Assche et al., 2003). A dose of 2 mg/kg has been shown to be as effective as 4 mg/kg. Patient response to this treatment has varied, with adverse effects causing withdrawal of treatment in some cases. However, some patients have stopped concurrent steroid therapy and have remained in remission for some time.

When patients with severe colitis fail to show a response to treatment with parenteral steroids, then ciclosporin at an intravenous dose of 2 mg/kg/day should be considered. If patients respond to parenteral ciclosporin they can subsequently be maintained on an oral dose for 3–6 months. If the patient has a low plasma magnesium (< 0.5 mmol/L) or low cholesterol (<3 mmol/L), they are at an increased risk of ciclosporin-induced seizures when given intravenously. In these circumstances, treatment with an oral ciclosporin preparation, for example, Neoral®, at a dose of 5 mg/kg/day is preferred. Ciclosporin therapy is used for many patients, but normally as a bridge to colectomy or starting maintenance treatment with azathioprine or mercaptopurine. Infliximab is an alternative 'rescue therapy' for acute severe colitis (NICE, 2008a) if ciclosporin is contraindicated or clinically inappropriate. A multi-centre randomised controlled trial (CONSTRUCT) is underway comparing the clinical and cost-effectiveness of infliximab and ciclosporin in the treatment of steroid resistant acute severe colitis.

Forty percent of patients who receive ciclosporin develop minor side effects such as tremor, paraesthesia, headache, gum hyperplasia, burning sensations of the hands and feet and hirsutism. Major complications include nephrotoxicity, neurotoxicity, hepatotoxicity and hypertension. There has been 1–2% mortality reported in some case series. Ciclosporin blood levels should be monitored and maintained within the range of 100–200 ng/mL. Grapefruit juice, macrolide antibiotics (mainly erythromycin and clarithromycin), ketoconazole, fluconazole, itraconazole, diltiazem, verapamil, oral contraceptives and protease inhibitors are just some of the drugs that increase ciclosporin levels and toxicity.

In severe proctitis, refractory to standard treatments, ciclosporin enemas have been used with some success at a dose of 250 mg at night for 1 month. No commercial preparation is available.

Tacrolimus. Tacrolimus is an alternative calcineurin inhibitor to ciclosporin that has shown some benefit in inducing remission in ulcerative colitis. It is of limited value in Crohn's disease.

Mycophenolate. It has been suggested that mycophenolate mofetil is effective and well tolerated in IBD. Although used if other treatments have failed, there is little evidence regarding its use in clinical practice.

Monitoring of immunosuppressants. Major concerns about the use of immunosuppressive agents are related to bone marrow suppression and hepatotoxicity. Therefore, patients should be monitored regularly and have routine blood counts and liver function tests including plasma bilirubin and alkaline phosphatase. These should be undertaken every 2–3 weeks for the first 2–3 months and then bimonthly. Although often advised, there is no evidence that more frequent monitoring is more effective. Patients should be taught to recognise the signs of bone marrow suppression and educated about the need for earlier blood tests and the increased risk of infection due to immunosuppression. It is recommended that all patients initiated or maintained on immunosuppressants are provided with a record card detailing current dose and blood test results. This should be shown to their doctor and pharmacist at each visit. There should be good shared care policies in place between primary and secondary care in the management of patients on immunomodulators.

The incidence of lymphomas in patients receiving immunosuppressants when compared with other treatments is of concern. Patients should be advised to avoid live vaccines while taking immunosuppressants, including corticosteroids. Guidance on appropriate action following abnormal blood results is provided in Box 13.2.

Biologic agents

Since their introduction over a decade ago, biological therapy targeting tumour necrosis factor alpha (TNF-α) has revolutionised the management of IBD. These agents are efficacious in treating signs and symptoms of Crohn's disease and ulcerative colitis, reducing corticosteroid requirements and draining fistulae, achieving mucosal healing and reducing the need for major abdominal surgery or hospitilisation. They are indicated for patients who have failed or are intolerant or who have contraindications to conventional therapy including corticosteroids and immunomodulators. Not all patients will require biological therapy which is expensive and is a significant cost to the Health Service. Some patients may derive greater benefit from early use of these agents such as patients who are steroid dependant or who have complex fistulising disease.

Biologic agents that are licensed for use in IBD are infliximab (Remicade®) and adalimumab (Humira®). At present there are no direct comparative studies of the two agents. Certolizumab pegol (Cimzia®) has also shown benefit and is an alternative in some cases; however, it is currently not licensed for use in IBD. All these monoclonal antibodies inhibit the functional activity of the pro-inflammatory cytokine TNF-α which damages cells lining the gut, causing pain, cramping and diarrhoea. Colonic biopsies post-treatment with these agents show a substantial reduction in TNF-α and a reduction in the commonly elevated plasma inflammatory marker C-reactive protein. Table 13.6 summarises the anti-TNF agents used. All appear to have similar efficacy, although there are more data on infliximab than adalimumab or certolizumab. Natalizumab, another monoclonal antibody, has also shown promise in treating active Crohn's disease. It works by inhibiting the migration of leucocytes into the CNS thereby reducing inflammation. It is unlicensed in IBD.

Box 13.2 Guidance on dealing with abnormal blood results for patients on immunosuppressant therapy

Baseline U&Es, LFTs and FBC should be carried out prior to initiation of therapy. These should be repeated at 2 weeks, 4 weeks then every 2–3 months.

Methotrexate should be *stopped* and the relevant expert advice obtained if any of the following occur:

WBC	$<4 \times 10^9\ L^{-1}$
Neutrophils	$<2 \times 10^9\ L^{-1}$
Platelets	$<150 \times 10^9\ L^{-1}$
AST/ALT	>3 × normal range

- Unexplained respiratory symptoms, for example, dyspnea, dry cough, especially if accompanied by fever and sweats
- Renal impairment
- Mouth or throat ulceration/rash/unexplained bleeding/fever/alopecia/recurrent sore throats, infections, fever or chills/nausea/vomiting/diarrhoea

Azathioprine or mercaptopurine should be *stopped* and the relevant expert advice obtained if any of the following occur:

WBC	$<4 \times 10^9\ L^{-1}$
Neutrophils	$<2 \times 10^9\ L^{-1}$
Platelets	$<150 \times 10^9\ L^{-1}$
AST/ALT	>3 × normal range

- Significant reduction in renal function
- Mouth or throat ulceration/rash/unexplained bleeding/fever/upper abdominal or back pain/alopecia/recurrent sore throats, infections, fever or chills/nausea/vomiting/diarrhoea
- Nausea may be relieved by taking the dose with/after food or in divided doses

Ciclosporin should be *stopped* and the relevant expert advice obtained if any of the following occur:

- High blood levels (will require dose adjustment)
- Significant reduction in renal function
- Uncontrolled hypertension

Drug blood levels should be done at similar intervals to FBC. A 12-h trough level should be taken, that is, before a dose. Target level within the range of 100–200 ng/mL. It takes 2–3 days to reach steady state after dose change

U&Es, urea and electrolytes; LFTs, liver function tests; FBC, full blood count; WBC, white blood cells; ALT, alanine transaminase; AST, aspartate transaminase.

Table 13.6 Summary of anti-TNF agents used in IBD

Agent	Licensed/(unlicensed) indication	Dose
Infliximab	*Crohn's disease*	
	Induction of remission in severe active disease	5 mg/kg intravenously at weeks 0 and 2
	Maintenance treatment	5 mg/kg intravenously 6 weeks after initial dose then every 8 weeks or further dose of 5 mg/kg if signs and symptoms recur
	Fistulising	5 mg/kg intravenously at weeks 0, 2 and 6 (consult product literature)
Infliximab	*Ulcerative colitis*	
	Induction of remission in moderate to severe active disease	5 mg/kg intravenously at weeks 0, 2 and 6
	Maintenance of remission in severe active disease	5 mg/kg intravenously every 8 weeks; discontinue if no response 14 weeks after initial dose
	Extra-intestinal manifestations (unlicensed)	5 mg/kg intravenously
Adalimumab	*Crohn's disease*	
	Induction of remission in severe active disease	80 mg subcutaneously at week 0, 40 mg at week 2 and or accelerated regime of 160 mg at week 0, 80 mg at week 2
	Maintenance treatment	40 mg subcutaneously on alternate weeks, increasing to weekly if loss of response
Certolizumab pegol	*Crohn's disease (unlicensed)* Used in moderate to severe disease when patients who have lost response to or are intolerant of infliximab or adalimumab	
	Induction	400 mg subcutaneously at weeks 0, 2 and 4
	Maintenance treatment	400 mg subcutaneously every 4 weeks

National guidance has been issued on the use of infliximab in ulcerative colitis (NICE, 2008a,b) and infliximab and adalimumab in the treatment of Crohn's disease (NICE, 2010). The latter guidance indicates treatment should be started with the less expensive drug, taking into account drug administration costs, required dose and product price per dose. This may need to be varied for individual patients due to differences in the method of administration and treatment schedules.

A combination of infliximab with azathioprine has been shown to be superior to monotherapy in inducing remission and mucosal healing in Crohn's patients naïve to both agents. The rate of infliximab-related infusion reactions was also less with combination treatment and there was no significant difference seen with the rate of serious infection (Colombel et al., 2010). For scheduled treatment, the concomitant immunomodulator should be reviewed and stopped after 6–12 months. It remains unclear whether the same applies to other anti-TNF agents. In practice, the same principles apply with other immunomodulators such as methotrexate.

Natalizumab should not be combined with an immunosuppressant or prolonged steroids as this may increase the risks of progressive multifocal leucoencephalopathy (D'Haens et al., 2010).

There is currently no specific guidance on how long anti-TNF agents should be continued for. Preliminary evidence suggests that many patients in clinical remission for greater than 1 year, with a normal C-reactive protein and complete mucosal healing on endoscopy will remain in remission during the following year after stopping treatment. Whether remission is then sustained or whether the behaviour of disease is altered in the long term is currently unknown (D'Haens et al., 2010). NICE guidance on the treatment of Crohn's disease recommends that infliximab or adalimumab treatment should be given until treatment failure (including the need for surgery) or until 12 months after initiation of treatment, whichever is shorter. Patients should then have their disease reassessed and continue treatment if there is clear evidence of ongoing active disease and treatment is still clinically appropriate. Treatment can be restarted if patients subsequently relapse.

Loss of response or intolerance to anti-TNF agents can be managed by optimising dosing regimes, switching to agents or switching class, for example, to natalizumab. Reasons for a loss of response should be assessed.

Monoclonal antibodies are contraindicated in patients with tuberculosis (TB) and, therefore, all patients should have a chest X-ray prior to administration to exclude latent TB. Infliximab increases the risk of TB five-fold. Other contraindications include moderate to severe cardiac failure, history of malignancy (excluding non-melanoma skin cancer), sepsis (including pelvic or perianal), optic neuritis. Intestinal stricturing is a relative contraindication (obstruction may be exacerbated through rapid healing at the stricture site) along with chronic hepatitis B/C carriers, primary failure or absence of inflammatory activity (normal C-reactive protein). Patients who receive live vaccines should not receive biological therapy for 3 months. Patients on biologics should be vaccinated against tetanus, pneumococcus species, influenza and hepatitis B. Young females should also be vaccinated for the human papilloma virus.

Anti-TNF agents should only be prescribed by a gastroenterologist with experience of IBD, and in the case of infliximab, administered in a setting where there are adequate resuscitation facilities available and patients are closely monitored. Patients self-administering adalimumab at home should be counselled on how to recognise signs of infection, for example, fever, productive cough, toothache, stinging on passing urine or if neurological symptoms develop.

Infliximab. Infliximab is a chimeric human murine monoclonal antibody, licensed for treating severe active Crohn's disease (with or without fistulae) which is refractory or intolerant to corticosteroids or conventional immunosuppressants alone or if surgery is inappropriate. Treatment may be repeated if the condition responded to the initial course but subsequently relapsed. Infliximab is also licensed for moderate to severe active ulcerative colitis (acute exacerbation) requiring hospitilisation and/or possible surgical intervention and if unresponsive to conventional treatments. Infliximab may half the need for colectomy in steroid refractory patients with acute ulcerative colitis. It remains to be determined whether infliximab is superior to ciclosporin (D'Haens et al., 2010).

In severe active Crohn's disease, infliximab is administered by intravenous infusion, at a dose of 5 mg/kg over a 2-h period, repeated after 2 weeks. If a clinical response is seen, then a maintenance dose of 5 mg/kg every 8 weeks should be given. Alternatively, a dose could be given when signs and symptoms recur. Fixed interval dosing may be superior to intermittent dosing because of the reduced risk of immunogenicity (NICE, 2010).

In active fistulising Crohn's disease where disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive therapy) or who are intolerant or have contraindications to conventional therapy, an initial dose of 5 mg/kg is given, repeated at 2 and 6 weeks after the first infusion is given. If no response is seen after three doses, no further treatment should be given (NICE, 2010).

Trials in inflammatory Crohn's disease have shown an 81% response rate at 4 weeks. After 12 weeks, 48% of patients still had a response. In fistulising disease, 68% of patients experienced a 50% reduction in the number of draining fistulas at two or more consecutive visits. If a loss of response is seen the dose can be increased to 10 mg/kg (unlicensed) or the dosing interval shortened. An alternative is to switch treatment to adalimumab.

In treatment-refractory, moderate to severe acute exacerbation of ulcerative colitis, the licensed dose regimen is 5 mg/kg at weeks 0, 2 and 6. The optimal maintenance strategy after induction therapy is currently unknown. Treatment should be discontinued if no response is seen after 14 weeks. In azathioprine naïve patients responding to infliximab induction, azathioprine is an option instead of infliximab for maintenance (Travis et al., 2008). Although unlicensed, infliximab has shown to be of benefit in extra-intestinal manifestations such as pyoderma gangrenosum and peripheral and axial naturopathies

All doses should be preceded with intravenous corticosteroid (hydrocortisone 200 mg) unless the patient has been taking an immunosuppressant for more than 3 months.

In some patients, infliximab has been associated with either infusion (during or shortly after infusion) or delayed hypersensitivity reactions. It may also affect the normal body immune responses in a significant number of patients. Other side effects include headache, dizziness, nausea, rash, raised liver function tests, abdominal pain, fatigue, etc.

Adalimumab. Adalimumab is a fully humanised anti-TNF monoclonal antibody which is licensed for the treatment of severe active Crohn's disease in patients who are refractory or intolerant to corticosteroids and conventional immunomodulators. It may also be used in those patients who have primary or secondary non-response to infliximab or developed a hypersensitivity reaction. Unlike infliximab it is not licensed for acute ulcerative colitis.

As adalimumab is fully humanised it is less immunogenic than infliximab. It also has the advantage of being given as a subcutaneous injection which enables patients to self-administer at home, therefore reducing nursing time and hospital bed occupancy. This also lends itself to supply by home delivery services. The licensed dose is an initial induction of 80 mg followed by 40 mg at week 2 and then 40 mg on alternate weeks thereafter as maintenance. An accelerated dose of 160 mg followed by 80 mg and then 40 mg on alternate weeks maintenance is more commonly used, particularly in those patients who have previously been on infliximab. The maintenance dose can be increased to 40 mg weekly if a diminished or suboptimal response is seen but treatment should be stopped if no response is seen within 12 weeks of the initial dose.

Infliximab may be of benefit in patients initiated on adalimumab as the first-line anti-TNF agent but who lose response to, or develop adverse effects. The efficacy of infliximab in patients with no initial response to adalimumab needs to be evaluated.

Certolizumab. Certolizumab is a pegylated monoclonal antibody fragment TNF-α antibody. It is currently used for those patients who have lost response to or have become intolerant to infliximab or adalimumab. It is given at an induction dose of 400 mg subcutaneously at weeks 0, 2 and 4 and then if a response is seen, once every 4 weeks as maintenance.

Antibiotics

Metronidazole has been used in Crohn's disease associated with perianal disease, sepsis associated with fistulae, perforation and bacterial overgrowth in the small bowel. Doses of 0.6–1.5 g/day are typically used and well tolerated. Metronidazole appears to be ineffective in ulcerative colitis. The associated paraesthesia appears to be dose related, occurring frequently with treatment of greater than 3 months duration. In such patients, doses should be gradually reduced or the drug alternated with another antibiotic, for example, ciprofloxacin, tetracycline or rifabutin, which have shown some limited benefit. The metabolite of metronidazole has a free nitro group and this is probably responsible for the drug's local activity. It also inhibits phospholipase A, contributing to a reduction in damage induced by polymorphonuclear leucocytes.

Other antibacterials are used if specifically indicated, especially when the causative bacterial agents have been identified.

Pseudomembranous colitis caused by *C. difficile* usually occurs after prolonged or multiple antibiotics. This can be distinguished from other causes of colitis by biopsy and stool culture. If it is unclear whether a patient has pseudomembranous or acute colitis, treatment with metronidazole or vancomycin and steroids is advised. A colonoscopy can be performed once symptoms resolve.

Other treatments

Thalidomide. The use of thalidomide, under specialist supervision, is restricted to refractory cases of Crohn's disease. Thalidomide acts as a TNF-α inhibitor and probably stabilises lysosomal membranes. At therapeutic doses it also inhibits the formation of superoxide and hydroxyl radicals, both potent oxidants capable of causing tissue damage. Daily doses in the range of 50–400 mg have proved beneficial when used for periods of 1 week to several months. Side effects during treatment include sedation, dry skin and reduced libido. Thalidomide is teratogenic and should never be used in women of child-bearing age.

Antidiarrhoeals. Codeine diphenoxylate and loperamide should be used with caution to treat diarrhoea and abdominal cramping in IBD. Their use may mask inflammation, infection, obstruction or colonic dilation, thereby delaying correct diagnosis.

Colestyramine. Colestyramine has been used in Crohn's disease following ileal resection to reduce diarrhoea associated with bile acid malabsorption caused by the decrease in small bowel absorptive surface area and the cathartic effect of bile salts on the colon. Doses of up to 4 g three times a day inhibit the secretion of water and electrolytes stimulated by bile acids.

Fish oils (omega-3 fatty acids). Fish liver oils containing eicosapentaenoic and docosahexaenoic acids have been used with some success in the treatment of both ulcerative colitis and Crohn's disease. These products cause unpleasant regurgitation which renders them unpalatable in long-time use. Enteric-coated preparations have reduced this problem. It is thought that fish oils work by diverting fatty acid metabolism from leukotriene B4 to the formation of the less inflammatory leukotriene B5.

Miscellaneous treatments. There are many limited trials, studies and case series in the literature evaluating other therapies for ulcerative colitis and Crohn's disease. These include probiotics, sodium cromoglicate, bismuth and arsenic salts, sucralfate, nicotine, oxygen-derived free radical scavengers, somatostatin analogues, lidocaine, chloroquine, d-penicillamine, carbomers, antituberculous agents, heparin, aloe vera, probiotics and worm therapy (helminths). In general, these treatments are not recommended, although the variety illustrates the limitations of current therapy. When a patient is not responding to conventional agents, consideration should be given to referral to a specialist centre for a review of current therapy and a plan of future management. Alternative and complementary treatments, for example, acupuncture, aromatherapy may have a role.

Leukapheresis has been shown to have some benefit in patients with IBD. It involves removal of leucocytes from the blood, either through an adsorptive system or by centrifugation. In each system, venous blood is removed in a continuous flow, anticoagulated, processed to deplete the leukocytes and returned to the circulation (see NICE, 2005). Table 13.7 summarises the pharmacological profile of drugs used in adults with IBD.

Future treatments

Future therapy is focusing on the ability of drugs to target a specific point in the inflammatory process, such as TNF, interleukins (IL-10, 11, 12), T-cell surface antigens and stem cell transplantation.

Table 13.7 Pharmacological profile of drugs used in adults with inflammatory bowel disease

Pharmacological group	Daily dose	$t^{½}$ (h)	Metabolism
Steroids			
Hydrocortisone	125–250 mg as foam enema 100–400 mg in 0.9% w/v in sodium chloride intravenously	1.5	Hepatic metabolism 70% and 30% unchanged
Prednisolone	20–60 mg orally 20 mg as foam or liquid enema 5–10 mg as suppositories	3	Hepatic metabolism 70% and 30% unchanged
Budesonide	3–9 mg orally 20 mg as enema	2.8	90% hepatic metabolism
Aminosalicylates			
Mesalazine	500 mg–1.5 g as suppositories 1 g as enema 1.2–2.4 g orally	0.7–2.4	Local and systemic Hepatic acetylation, glucuronidation
Olsalazine	1–3 g orally	1.0	Local and systemic Hepatic acetylation, glucuronidation
Sulfasalazine	3 g as enema 1–2 g as suppositories 4–8 g orally	5–8	Colonic azo-reduction Local and systemic acetylation Hepatic glucuronidation
Balsalazide	3–6.75 g orally	1.0	Local and systemic hepatic acetylation
Antibiotics			
Metronidazole	600 mg–1.2 g orally 1.5 g intravenously	6–24	Hepatic metabolism
Immunosuppressants			
Azathioprine	2–2.5 mg/kg orally	3	Hepatic metabolism to 6-mercaptopurine
6-Mercaptopurine	1–1.5 mg/kg orally	1.5	Hepatic metabolism to inactive metabolite
Methotrexate	15–25 mg by intramuscular or subcutaneous injection weekly 15–25 mg orally weekly	3–10	Insignificant metabolism at low doses
Ciclosporin	2 mg/kg intravenously 5 mg/kg orally	19–27	Mainly hepatic metabolism
Monoclonal antibody			
Infliximab	5 mg/kg intravenous infusion every 8 weeks (maintenance)	8–9 days	Unknown
Adalimumab	40 mg subcutaneous injection every 2 weeks	10–19 days	Unknown
Certolizumab	400 mg subcutaneous injection every 4 weeks	14 days	Unknown
Miscellaneous			
Arsenic salts	250 mg–1 g rectally	72	Tissue deposition excreted unchanged
Bismuth salts	200 mg–1.2 g rectally	60–80	Tissue deposition excreted unchanged
Fish oils	3–4 g	None	Used in the arachidonic acid cycle
Sodium cromoglicate	200–800 mg orally 100–400 mg rectally	Unknown	Poorly absorbed, excreted unchanged in urine and bile
Nicotine	5–15 mg transdermally	0.5–2.0	Hepatic oxidation to cotinine 5% excreted unchanged
Lidocaine	200–800 mg rectally	1–2	Hepatic de-ethylation and hydrolysis 3% excreted unchanged Largely excreted unchanged
Human growth hormone	1.5–5 mg daily by subcutaneous injection	0.5–4	Unknown
Thalidomide	100–400 mg orally	7–16	Hydrolysis
Colestyramine	4–12 g orally		Not absorbed
Probiotics, for example, VSL#3	1–2 sachets daily orally		Poorly absorbed

Surgical treatment

Fifty to eighty percent of Crohn's disease patients will require surgery within 5–10 years of diagnosis. In contrast, 20–30% of ulcerative colitis patients will usually undergo colectomy with 5 years.

In ulcerative colitis, surgical colectomy, temporary ileostomy and ileoanal pouch construction are all curative. These are the surgical interventions of choice, although proctocolectomy and permanent ileostomy also have a role. Curative surgery is not possible in Crohn's disease as recurrence elsewhere in the gut is inevitable. Complications in the course of their illness result in about 70% of patients with Crohn's disease requiring at least one surgical procedure. If a significant length of gut is removed this can result in short gut syndrome which may require long-term parenteral nutrition and medication to control a high-output stoma if present, for example, PPIs, loperamide, codeine phosphate, isotonic fluids.

Patient care

The impact of a diagnosis of IBD should not be underestimated. In general, most patients are diagnosed when they are relatively young and the disease can have a significant effect on the rest of their life. In addition to managing symptoms, the condition can result in loss of education and difficulty in gaining employment or insurance. In young patients, it can cause psychological problems and growth failure or retarded sexual development. Anxiety and loss of self-esteem are commonly described. In addition to pharmacological treatments, psychological support is also important. Medical treatment with corticosteroids and immunosuppressants causes secondary health problems such as infection and surgery may result in complications such as intestinal failure. The care of patients with IBD is, therefore, a challenge for the multidisciplinary team.

All patients should be educated about their illness and medication and reminded that even in periods of remission it is important to continue taking prescribed therapy. This should take the form of verbal and written information. Drug use is invariably lifelong and patients are likely to receive several different treatments during the course of their illness due to intolerance or lack of response. Certain patients such as female or those newly diagnosed patients may require more tailored information about the condition or treatment. Patients with poor dexterity may find the use of rectal preparations difficult and these preparations may, therefore, be poorly tolerated. Leaflets about IBD and insurance or employment for patients with IBD have been prepared by the National Association for Colitis and Crohn's Disease (www.nacc.org.uk). Patients should also be warned about unreliable information sources.

Patients and primary care doctors may require additional reassurance as several of the treatments used, for example, azathioprine, are unlicensed for IBD. Regular blood monitoring of aminosalicylates and immunosuppressants is essential to ensure patients avoid toxicity associated with these drugs. All patients taking steroids must be issued with a steroid card. Shared care policies between primary care doctors, gastroenterologists and patients may also be appropriate.

If relapse occurs in some patients, they are advised to increase the dose of their current oral therapy and/or commence rectal administration of a corticosteroid before contacting their doctor. If symptoms do not improve within 48 h they should arrange a review with their specialist.

Effective home treatment of proctitis is important because tenesmus and occasional faecal incontinence, apart from being distressing, limit further treatment. Good counselling on the administration of topical therapy is important to ensure effectiveness and adherence.

IBD affects young adults, so pregnancy is not uncommon. Poorly controlled IBD can affect fertility and pregnancy. Good nutrition, stopping smoking and adherence to medication is important. Active disease is a risk factor for pre-term delivery and low birth weight. Infertility associated with sulfasalazine therapy would indicate the use of alternative aminosalicylate therapy. With the exception of methotrexate, which is contraindicated in pregnancy, most drugs used in the treatment of IBD do not present a significant hazard. However, patients are strongly advised to first discuss any plans for pregnancy with their gastroenterologist. Care of pregnant women should be done jointly by a gastroenterologist and obstetrician.

Encouraging patients to stop smoking, especially those with Crohn's disease, can have a significant impact on the course of the disease.

Long-term steroid use and underlying IBD both contribute to a higher risk of developing osteoporosis. This is prevalent in up to 50% of the patient population with IBD. Patients with Crohn's disease appear more susceptible to osteoporosis than those with ulcerative colitis. Regular DEXA-scanning should be considered and preventive treatment with bisphosphonate and/or calcium and vitamin D supplements may be necessary. Guidance for the treatment of osteoporosis in IBD has been published by the British Society of Gastroenterology.

IBD patients often develop microcytic anaemia because of malabsorption and chronic blood loss. Assessment of the blood film and serum ferritin can differentiate between iron deficiency and anaemia of chronic disease. Oral iron supplements are generally poorly tolerated and parenteral iron may be required. Guidance of the treatment of iron-deficiency anaemia in IBD has been published (Gasche et al., 2007). Megaloblastic anaemias are uncommon, although vitamin B_{12} and folate deficiencies occur and may benefit from appropriate supplementation.

The European Crohn's and Colitis Organisation have published evidence-based consensus guidelines on the prevention, diagnosis and management of opportunistic infections in IBD (Rahier et al., 2009). These highlight which vaccinations should be offered on diagnosis of IBD. UK practice currently recommends influenza, and pneumococcal vaccine in immunosupressed patients only, along with HPV vaccines for females aged 12–18 years in line with other national guidelines. IBD patients in the UK are also advised to receive the swine flu vaccine if immunocompromised.

In 2009, National IBD Standards were published by key stakeholders involved in the care of patients with IBD to improve the service provided for people with a diagnosis of IBD across the UK. The aim of the standards is to ensure patients receive consistent, high-quality care and that IBD services throughout the UK are evidence based, engaged in local and national networking, based on modern IT and audit, meet specific minimum standards. The delivery of patient-focused care requires a multidisciplinary approach which should comprise medical gastroenterologist, nurse specialist, pharmacist, dietician, psychologist, colorectal surgeon, primary care doctor, radiologist and histopathologist.

Case studies

Case 13.1

Miss A has been receiving maintenance treatment with infliximab for Crohn's disease for the last 6 months but is now losing response and the decision is made to switch her to adalimumab. She weighs 65 kg and is currently taking azathioprine 100 mg daily and Adcal D_3 two tablets daily. She is hoping to start a family within the next year.

Questions

1. What dose of adalimumab (Humira®) should be prescribed?
2. For how long should combination treatment with azathioprine and adalimumab (Humira®) continue?
3. What advice would you give regarding immunisation for patients on biologic agents?
4. Is adalimumab (Humira®) safe in pregnancy and breastfeeding?

Answers

1. The licensed dosing schedule for severe active Crohn's disease is 80 mg, then 40 mg 2 weeks after initial dose or an accelerated regimen (more commonly used in practice) of 160 mg followed by 80 mg 2 weeks after initial dose; the maintenance dose is 40 mg on alternate weeks, increased if necessary to 40 mg weekly. Treatment should be reviewed if no response is seen within 12 weeks of the initial dose. Adalimumab is administered by subcutaneous injection.
2. The risk of developing immunogenicity and loss of response to adalimumab must be balanced against potential toxicities of combining biologic agents with immunosuppressants such as azathioprine. There is no definitive duration of overlap but a period of 6 months is common and then the immunomodulator can be stopped.
3. Patients should have annual vaccination against influenza (seasonal flu) and swine flu. Pneumococcal polysaccharide vaccine (doses at 0 and 3 years) is also recommended as anyone who gets a viral pneumonia when they are immunocompromised is at high risk of pneumococcal co-infection.
4. As adalimumab is a relatively new drug, little is known about its effect in pregnancy. The manufacturer advises to avoid and take adequate contraception during and for at least 5 months after the last dose. Patients should be advised that if they are planning a pregnancy or are already pregnant and are receiving adalimumab then they must inform their specialist. Adalimumab has been assigned to pregnancy category B by the FDA. Animal studies have revealed no teratogenic, embryotoxic or fetotoxic effects. There are no controlled data in human pregnancy. Adalimumab is only recommended for use during pregnancy when benefit outweighs risk. To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established.

   The priority is to keep the mother well and in remission. Although very low amounts of adalimumab may be transferred into breast milk, there is no risk to the baby, because adalimumab is a protein that is digested, so cannot be absorbed. The benefits of breastfeeding generally outweigh any theoretical risk while using adalimumab. Information changes rapidly, so it is important to discuss this with a specialist gastroenterologist.

Case 13.2

Miss B, a 30-year-old woman has a known history of ulcerative colitis and presents with bloody diarrhoea (12 motions/day), pyrexia, CRP 84 mg/L, platelets 545 × 10^9 L^{-1}, haemoglobin 10.5 g/dL. She is admitted to hospital for intensive medical management with intravenous and rectal steroids, fluid and electrolyte replacement and subcutaneous heparin.

Questions

1. What is the rationale for prescribing Miss B intravenous steroids and what biochemical monitoring should be undertaken?
2. Miss B is complaining of abdominal pain and the doctor is considering starting codeine phosphate or diclofenac. What advice would you give them?

   By day 3 of intensive therapy, Miss B is still passing more than six stools a day and her C-reactive protein remains greater than 45 mg/L. The decision is made to start infliximab. The patient weighs 65 kg.
3. What assessments should be made prior to administering infliximab?
4. What dose would you recommend and what advice would you give the nursing staff about administration?

Answers

1. Intravenous administration is appropriate as absorption of oral steroids could be erratic and unpredictable in severe inflammation or in patients who are systemically unwell. A parenteral steroid also ensures rapid attainment of drug levels. The mineralocorticoid properties of hydrocortisone may cause sodium and water retention, and hypokalaemia and glucocorticoid property may produce a rise in blood sugar levels. In case the patient requires second-line treatment with ciclosporin, a magnesium level and cholesterol level should be done.
2. Regular use of opiates such as codeine phosphate should be avoided as the resulting reduction in gastro-intestinal motility may precipitate a toxic megacolon and perforation. For this reason, antidiarrhoeal agents such as loperamide should also be avoided. NSAIDs, by reducing cyclo-oxygenase enzyme activity, may potentially increase production of proinflammatory leukotrienes and increase bleeding. Paracetamol is safe and may be prescribed. The anti-inflammatory action of the intravenous steroids should also reduce pain. However, pain is uncommon in ulcerative colitis because the inflammation is mucosal. The patient should be reviewed to ensure perforation is not overlooked.
3. Definite contraindications to anti-TNF therapy are sepsis, including pelvic or perianal sepsis, TB, optic neuritis or other demyelinating disorders, infusion reactions (previous sensitivity to either agent or murine products), cancer (past or present) or cardiac failure (moderate to severe NYHA III or IV – marked limitation of physical activity). Relative contraindications are pregnancy or breastfeeding, obstructive structuring disease

or surgery potentially inappropriate, chronic hepatitis B or C carriers, primary failure or loss of response, absence of inflammatory activity, that is, normal C-reactive protein.

A chest X-ray should be carried out +/− Mantoux test to rule out latent TB as infliximab increases the risk of TB five-fold. Indian or African ethnicity escalates the risk.

4. A 5 mg/kg dose should be prescribed (5 × 65 kg = 300 mg to the nearest whole vial) and infused over 2 h.

Rare infusion-related side effects are hypotension, shortness of breath and flushing. Blood pressure and pulse should be monitored every 30 min. Stopping the infusion temporarily often resolves the symptoms or they can be treated with antihistamines and paracetamol. Anaphylactic reactions are very rare but have been reported. If anaphylaxis occurs then future infusions are not advised. The patient is already receiving IV steroids to minimise the risk of hypersensitivity. Other side effects include lower respiratory tract infection and fatigue.

Case 13.3

Mr C was diagnosed with ulcerative colitis 12 months ago. His past medical history includes surgical resection and radiotherapy for squamous cell carcinoma of the mouth. As a result of this the patient has a Peg-J tube inserted for administration of enteral feed and medication. He is currently prescribed Pentasa® 2 g/day and a reducing course of prednisolone.

Question

1. Is Pentasa® suitable for administration via a Peg-J tube?

Answer

1. Pentasa® MR tablets disperse in water to give M/R granules which are slightly smaller than those in the sachets. However, the tablet contents can only be drawn into a catheter-tipped syringe owing to their size and will only flush down a 16 fr tube without blockage. The granules must not be crushed as this will destroy the modified release mechanism. As Peg-J tubes are typically smaller than 16 fr this preparation is unsuitable for Mr C as are all other oral modified release 5-ASA preparations. An alternative would be topical preparations if clinically appropriate or to consider changing to sulfasalazine liquid preparation.

Case 13.4

Mrs D is admitted to hospital for colectomy and formation of an ileostomy, following unsuccessful medical management of her ulcerative colitis. Her regular drug therapy on admission includes:
Pentasa® 1 g three times a day
Azathioprine 100 mg daily
Prednisolone 5–15 mg/day
Digoxin 125 µcg daily
Aspirin 75 mg daily

Questions

1. Following her operation, Mrs D's ileostomy output is high. What treatment approaches are available for managing high-output stomas?
2. What changes, if any, would you recommend to her current prescription?

Answers

1. High-output stomas lead to dehydration and metabolic disturbance, for example, hypokalaemia, hypernatraemia. Drinking more can make the situation worse since this flushes the small intestinal contents through and exacerbates dehydration. Food and drink can promote secretion and increase volume.

The causes of high-output stomas need to be considered and may include high lactose intake, partial obstruction, gastric hypersecretion, inappropriate diet, laxatives and diuretics. Treatment options should include high-dose PPI to reduce gastric acid hypersecretion and codeine phosphate (180–240 mg/day) and/or loperamide to reduce gut motility. In the absence of a colon, a dose of loperamide that exceeds 16 mg/day can be used without adverse effect. Octreotide has been used as an alternative to the antimotility drugs but would appear to offer limited benefit and is best reserved for when other measures have been tried. Intake of isotonic fluids with a sodium concentration >90 mmol/L, to allow the jejunum to absorb water, may also be of benefit.

2. As ulcerative colitis is confined to the colon, following colectomy, the patient will no longer require medical treatment for maintenance of her ulcerative colitis, that is, Pentasa® and azathioprine and these can be stopped. Depending on how long the patient has been taking prednisolone, this should be reduced slowly to prevent withdrawal. If the stoma output remains high, careful monitoring of potassium levels should be taken to prevent digoxin toxicity. If potassium supplementation is given, oral modified release preparations should be avoided.

Case 13.5

Mr E was diagnosed with Crohn's disease 4 years ago and also suffers from gout. Although relatively well, during the last year he has required two courses of prednisolone. However, when the dose has been reduced, his symptoms have flared. The decision has been made to start Mr F on azathioprine. He weighs 70 kg.

Questions

1. What dose of azathioprine would you recommend for this patient to re-establish remission?
2. Are there any drugs Mr F should avoid while taking azathioprine?

Answers

1. A dose of 2–2.5 mg/kg should be recommended (150–175 mg). As azathioprine is a steroid-sparing agent this should enable prednisolone to be withdrawn.
2. One of the most significant drug interactions is with allopurinol which inhibits the principal pathway for detoxification of azathioprine and mercaptopurine. Patients receiving allopurinol concomitantly should have their dose of azathioprine reduced to approximately one-third to a quarter of the usual dose. NSAIDs which are often used to treat an acute flare of gout should be avoided in Crohn's disease.

Case 13.6

Mrs F, a 36-year-old woman, is unable to tolerate azathioprine or mercaptopurine for her Crohn's disease and has been started on oral methotrexate 25 mg once weekly.

Questions

1. What counselling points would you discuss with the patient regarding her methotrexate treatment?

2. What is the rationale for also prescribing folic acid?
3. Mrs F asks you if it is safe to become pregnant while taking methotrexate. What advice would you give her?

Answers

1. Methotrexate is effective in maintaining remission in Crohn's disease in patients who do not respond to or tolerate azathioprine or mercaptopurine. Like the thioguanines it has inflammatory and immunosuppressive properties which help to reduce the damage to the bowel wall which is responsible for the symptoms of Crohn's disease. It can take several weeks before patients start to feel the effects.

   Methotrexate should be taken once a week, on the same day of the week. Methotrexate is never taken every day. Methotrexate comes in tablet form in two different strengths: 2.5 and 10 mg. The two strengths are different shapes but are a similar colour. It is important that patients keep an up to date record of the dose they are taking and always check the strength of the tablet they have been given each time they get a prescription. To reduce the risk of confusion and possible overdose, many pharmacies only stock 2.5 mg strength tablets. If patients have problems swallowing large numbers of tablets (in this case 10 × 2.5 mg), they can be dispersed in water. As recommended by the NPSA (2006) in their 'Improving compliance with oral methotrexate' guidelines, patients should be given a monitoring card which details the dose, strength and quantity of tablets to be taken each week and blood test results.

   The most frequent side effects are nausea and vomiting (especially at start of treatment) which can be reduced by taking the dose with food; inflammation and soreness of the mouth, diarrhoea and rash or generalised itchiness. Hair loss can also occur but is reversible on stopping treatment.

   Mrs F should also be advised about the need for regular blood tests as methotrexate suppresses the bone marrow and can affect liver function. If they feel generally unwell or develop unexplained bruising, bleeding, sore throat, fever or malaise, they should contact their doctor. Methotrexate can cause inflammation in the lung tissue leading to a feeling of breathlessness or persistent cough. Although very rare, it should be reported to a doctor as soon as possible.

   Immunisation with live vaccines should also be avoided. Patient should receive vaccination for influenza, pneumococcal and swine flu.
2. Methotrexate is a folate antagonist. In patients who experience gastro-intestinal side effects, folic acid helps to reduce their frequency. It should be taken once weekly, 4 days after the methotrexate. As an aide memoire patients are often advised to take it on a Friday if they take methotrexate on a Monday.
3. It is not safe to take methotrexate during pregnancy. It is essential that men and women of child-bearing potential use a reliable form of contraception during treatment and for at least 3 months after treatment is stopped as methotrexate can damage the developing fetus. If patients are planning a family it is essential they discuss it with their doctor first.

Case 13.7

Mr G is newly diagnosed with mild ulcerative colitis. His abdominal X-ray suggests predominantly disease of the rectum and sigmoid colon. His past medical history includes joint stiffness due to rheumatoid arthritis. He presents at the pharmacy with a prescription for sulphasalazine tablets and Predfoam® one at night.

Questions

1. What advice would you give Mr G about the administration of Predfoam® enemas?
2. What are the side effects associated with the use of topical steroids?

   Mr G expresses concerns to the primary care doctor about the possibility of sulphasalazine impairing fertility as he and his wife hope to start a family. The primary care doctor decides to switch Mr G to mesalazine tablets, 800 mg taken three times a day.
3. Mesalazine 400 mg tablets are available in several different brands. Does it matter which brand is supplied?
4. Does mesalazine cause problems with fertility?

Answers

1. Rectal therapy is appropriate for mild left-sided disease. Enemas are best administered just before bedtime when the supine position allows longer retention times. Predfoam® comes in an aerosol can and the drug is delivered by attaching some plastic rectal tubes to the canister. A new tube is used for each dose. Patients with rheumatoid arthritis may have difficulty in using enemas and this may affect adherence and treatment success. The aerosol canister is flammable and care should be taken.
2. Prednisolone sodium metasulphobenzoate (Predfoam®) is poorly absorbed and the systemic side effects are minimal.
3. Once initiated, patients should remain on the same brand of mesalazine as different brands have different release profiles. Relapse of disease can occur if patients are inadvertently switched to another brand. Prescribers are encouraged to prescribe by brand and not by generic name.
4. Mesalazine does not cause problems with fertility, only sulfasalazine is associated with infertility and this only affects men. Sulfasalazine affects sperm but is reversible on stopping treatment.

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Useful websites

British Society of Gastroenterology, www.bsg.org.uk/

IBD standards, www.ibdstandards.org.uk/

Constipation and diarrhoea 14

P. Rutter

Key points

Constipation

- About 90% of people defaecate between three times a day and once every 3 days.
- Constipation is considered infrequent bowel action when it happens twice a week or less that involves straining to pass hard stools accompanied by a sensation of pain or incomplete evacuation.
- Constipation is usually not caused by a serious disease and is corrected by non-drug treatment.
- Non-drug treatment involves increasing fibre intake, increasing fluid intake and encouraging exercise.
- The four main groups of drugs used to treat constipation (bulk forming, stimulant, osmotic and faecal softener) all have proven efficacy compared to placebo.

Diarrhoea

- Diarrhoea is the passage of loose or watery stools, at least three times in a 24-h period, which may be accompanied by anorexia, nausea, vomiting, abdominal cramps or bloating.
- Gastroenteritis is the most common cause of diarrhoea in all age groups.
- In the UK, rotavirus and small round structured virus (SRSV) are the most common causes of gastroenteritis in children.
- In adults, Campylobacter followed by rotavirus are the most common causes.
- Blood in diarrhoea is classed as dysentery and indicates the presence of an invasive organism such as Campylobacter, Salmonella, Shigella or *Escherichia coli* O157.
- Dehydration is the main complication of acute diarrhoea. Oral rehydration solution is the mainstay of treatment, particularly in children and the elderly.
- Antimotility agents, for example, loperamide, diphenoxylate, codeine, may be given to adults with mild-to-moderate diarrhoea but are not recommended for use in children.

Constipation and diarrhoea are two of the most common disorders of the gastro-intestinal tract. Most adults will suffer from these disorders at some time in their life and while they are often self-limiting, they can cause significant morbidity or occur as a secondary feature to a more serious disorder. For example, constipation may be secondary to hypothyroidism, hypokalaemia, diabetes, multiple sclerosis or gastro-intestinal obstruction. Likewise, diarrhoea may be secondary to ulcerative colitis, Crohn's disease, malabsorption or bowel carcinoma. Both constipation and diarrhoea can also be drug induced and this should be considered when trying to identify a likely cause and determine effective management.

Constipation

In Western populations, 90% of people defaecate between three times a day and once every 3 days. It is clear, therefore, that to base a definition of constipation on frequency alone is problematic. What is perceived to be constipation by one individual may be normal to another. Most definitions of constipation include infrequent bowel action of twice a week or less that involves straining to pass hard faeces and which may be accompanied by a sensation of pain or incomplete evacuation. A pragmatic definition would simply be the passage of hard stools less frequently than the patient's own normal pattern. Standard criteria for the diagnosis of diarrhoea are available (Longstreth et al., 2006), although they are seldom used in practice.

Incidence

Constipation affects all age groups but is more common in the elderly: up to 20% of elderly people, compared to 8% of middle-aged and 3% of young people, seek medical advice for constipation. In the elderly, poor diet, insufficient intake of fluids, lack of exercise, concurrent disease states and use of drugs that predispose to constipation have all been identified as contributory factors.

Constipation is reported to be twice as common in women than men, although this probably reflects the greater likelihood that they seek medical advice. Constipation is, however, common in late pregnancy (up to 40% of women) due to increased circulating oestrogens, reduced gastro-intestinal motility and delayed bowel emptying caused by displacement of the uterus against the colon. It has also been reported that between 5% and 10% of children have constipation and it is more common in formula-fed babies.

Aetiology

The digestive system can be divided into the upper and lower gastro-intestinal tract. The upper gastro-intestinal tract starts at the mouth and includes the oesophagus and stomach and is

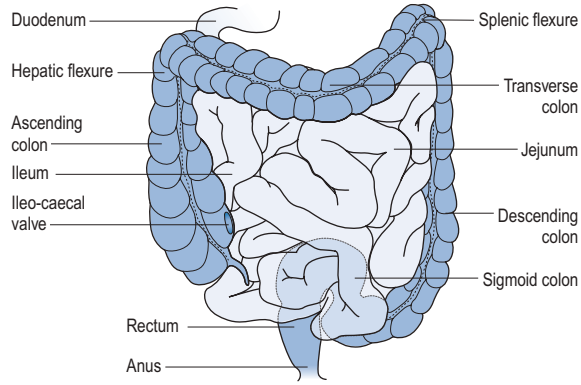

Fig. 14.1 The lower gastro-intestinal tract.

responsible for the ingestion and digestion of food. The lower gastro-intestinal tract consists of the small intestine, large intestine (colon), rectum and anus (Fig. 14.1) and is responsible for the absorption of nutrients, conserving body water and electrolytes, drying the faeces and elimination.

The remains of undigested food are swept along the gastro-intestinal tract by waves of muscular contractions called peristalsis. These peristaltic waves eventually move the faeces from the colon to the rectum and induce the urge to defaecate. By the time the stool reaches the rectum it generally has a solid consistency because most of the water has been absorbed.

Normally there is a net uptake of fluid in the intestine in response to osmotic gradients involving the absorption and secretion of ions, and the absorption of sugars and amino acids. This process is under the influence of the autonomic nervous system (sympathetic and parasympathetic). In those situations where absorption increases, this will generally lead to constipation, whereas a net secretion will result in diarrhoea.

Agents that alter intestinal motility, either directly or by acting on the autonomic nervous system, affect the transit time of food along the gastro-intestinal tract. Since the extent of absorption and secretion of fluid from the gastro-intestinal tract generally parallels transit time, a slower transit time will lead to the formation of hard stools and constipation. Motility is largely under parasympathetic (cholinergic) control, with stimulation bringing about an increase in motility while antagonists such as anticholinergics, or drugs with anticholinergic side effects, decrease motility and induce constipation. This mechanism is distinct from that of the other major group of drugs that induce constipation, the opioids. Opioids cause constipation by maintaining or increasing the tone of smooth muscle, suppressing forward peristalsis, raising sphincter tone at the ileocaecal valve and anal sphincter, and reducing sensitivity to rectal distension. This delays passage of faeces through the gut, with a resultant increase in absorption of electrolytes and water in the small intestine and colon.

It is normally the lower section of the gastro-intestinal tract that becomes dysfunctional during constipation. For convenience, many classify constipation as originating from within the colon and rectum, or externally. Causes directly attributable to the colon or rectum include obstruction from neoplasm, Hirschsprung's disease (absence of neurons in the diseased segment of the internal anal sphincter), outlet obstruction due to rectal prolapse or damage to the pudendal nerve, typically during childbirth. Causes of constipation outside the colon include poor diet, inadequate fibre intake, inadequate water intake, excessive intake of caffeine, use of medicines with constipating side effects or systemic disorders such as hypothyroidism, diabetic autonomic neuropathy, spinal cord injury, cerebrovascular accident, multiple sclerosis or Parkinson's disease.

Differential diagnosis

Constipation is a symptom and not a disease and can be caused by many different factors (Table 14.1) but the overwhelming majority of cases in non-elderly patients will be due to lack of dietary fibre. To aid diagnosis, questions need to be asked about the frequency and consistency of stools, nausea, vomiting, abdominal pain, distension, discomfort, mobility, diet and other concurrent symptoms or disorders the patient may be experiencing. It may also be necessary to ask about access to a toilet or commode. The individual with limited mobility may suppress the urge to defaecate because of difficulty in getting to the toilet. Likewise, lack of privacy or dependency on a nurse or carer for toileting may result in urge suppression that precipitates constipation or exacerbates an underlying predisposition. Patients with unexplained constipation of recent onset or a sudden aggravation of existing constipation associated with abdominal pain and the passage of blood or mucus, and long-standing constipation unresponsive to treatment require further investigation. Investigations include sigmoidoscopy/colonoscopy, barium enema, full blood count and biochemical monitoring including thyroid function tests (Fig. 14.2).

General management

In uncomplicated constipation, education and advice on diet and exercise are the mainstays of management and may adequately control symptoms in many individuals. Typically this advice will include reassurance that the individual does not have cancer, that the normal frequency of defaecation varies widely between individuals, and that mild constipation is not in itself harmful.

If the patient is taking medication for a concurrent disorder this must be assessed for its propensity to cause constipation. In the UK, over 700 medicinal products, including ophthalmic preparations, have constipation listed as a possible side effect. Common examples of medicines involved are presented in Table 14.2.

Non-drug treatment

Non-drug treatment is advocated as first-line therapy for all patient groups, except those who are terminally ill. This often includes advising an increase in fluid intake at the same time as reducing strong or excessive intake of tea or coffee, since these act as a diuretic and serve to make constipation worse.

Table 14.1 Causes of constipation

Cause	Comment
Poor diet	Diets high in animal fats, for example, meats, dairy products, eggs, and refined sugar, for example, sweets, but low in fibre predispose to constipation
Irritable bowel syndrome	Spasm of colon delays transit of intestinal contents. Patients have a history of alternating constipation and diarrhoea
Poor bowel habit	Ignoring and suppressing the urge to have a bowel movement will contribute to constipation
Laxative abuse	Habitual consumption of laxatives necessitates increase in dose over time until intestine becomes atonic and unable to function without laxative stimulation
Travel	Changes in lifestyle, daily routine, diet and drinking water may all contribute to constipation
Hormone disturbances	For example, hypothyroidism, diabetes. Other clinical signs should be more prominent, for example, lethargy and cold intolerance in hypothyroidism and increased urination and thirst in diabetes
Pregnancy	Mechanical pressure of womb on intestine and hormonal changes, for example, high levels of progesterone
Fissures and haemorrhoids	Painful disorders of the anus often lead patients to suppress defaecation, leading to constipation
Diseases	Many disease states may have constipation as a symptom, for example, scleroderma, lupus, multiple sclerosis, depression, Parkinson's disease, stroke
Mechanical compression	Scarring, inflammation around diverticula and tumours can produce mechanical compression of intestine
Nerve damage	Spinal cord injuries and tumours pressing on the spinal cord affect nerves that lead to intestine
Colonic motility disorders	Peristaltic activity of intestine may be ineffective, resulting in colonic inertia
Medication	See Table 14.2
Dehydration	Insufficient fluid intake or excessive fluid loss. Water and other fluids add bulk to stools, making bowel movements soft and easier to pass
Immobility	Prolonged bedrest after an accident, during an illness or general lack of exercise
Electrolyte abnormalities	Hypercalcaemia, hypokalaemia

It is generally recommended that fibre intake in the form of fruit, vegetables, cereals, grain foods, wholemeal bread, etc. be increased to about 30 g/day. The amounts of fibre in commonly eaten foods have been published (MeReC, 2004). Such a diet should be tried for at least 1 month to determine if it has an effect. Most will notice an effect within 3–5 days. Unfortunately, a high-fibre diet is not without problems, with patients complaining of flatulence, bloating and distension, although these effects should diminish over a period of several months. Patients who increase their fibre intake must also be advised to drink 2 L of water a day. Where an intake of this volume cannot be ingested it will be necessary to avoid increasing dietary fibre. An increased level of exercise should also accompany the raised fibre intake as this is thought to help relax and contract the abdominal muscles and help food move more efficiently through the gut.

A high-fibre diet is not recommended in those with megacolon or hypotonic colon/rectum because they do not respond to bulk in the colon. Similarly, a high-fibre diet may not be appropriate in those with opioid-induced constipation.

Drug treatment

Drug treatment is indicated where there is faecal impaction, constipation associated with illness, surgery, pregnancy, poor diet, where the constipation is drug induced, where bowel strain is undesirable, and as part of bowel preparation for surgery. The various laxatives available can be classified as bulk forming, stimulant, osmotic and faecal softeners. A systematic review (Tramonte et al., 1997) identified 36 trials involving 1815 participants that met their inclusion criteria. Twenty of the trials compared laxative against placebo or regular diet, 13 of which demonstrated statistically significant increases in bowel movement. The remaining 16 trials compared different types of laxatives with each other. The review concluded that laxative use was superior to placebo but due to a lack of comparative data could not conclude which laxative group was most efficacious. Further, more recent reviews have found good evidence that macrogols are effective, as are ispaghula husk and bisacodyl, although data is still lacking on which laxative is best (Frizelle and Barclay, 2007).

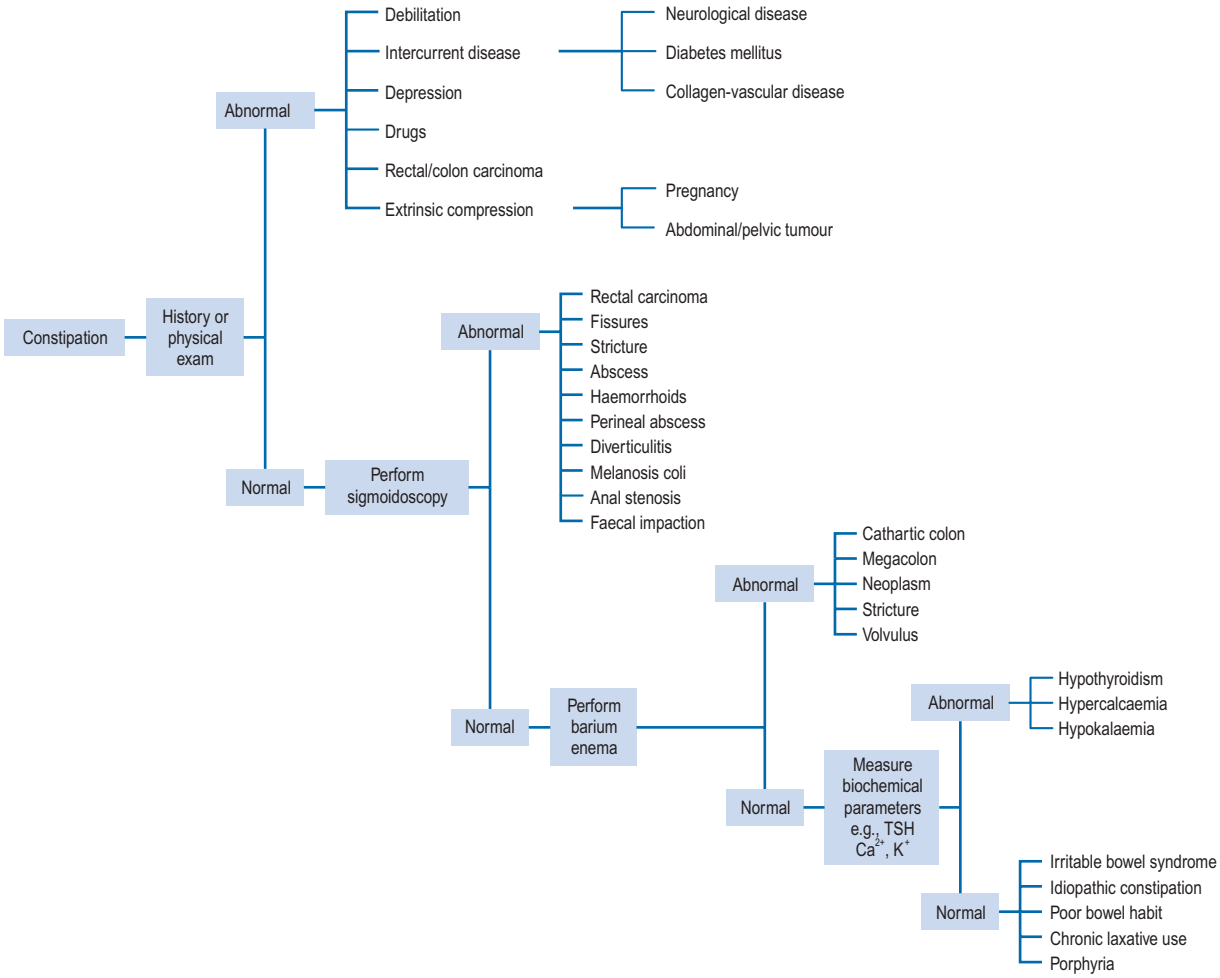

Fig. 14.2 A diagnostic algorithm for constipation.

In general, the fit, active, elderly person should be treated as a younger adult. In contrast, management of constipation in children is often complex. Early treatment is required in children to avoid developing a megarectum, faecal impaction and overflow incontinence. Encouraging the child to use the toilet after meals and increasing dietary fibre have a role alongside oral drug treatment. Depending on circumstances, behavioural therapy may be indicated. In pregnancy, if drug treatment is required, bulk-forming laxatives are first choice, but if stools remain hard then either changing to or adding in lactulose or a macrogol is advocated. Conversely, if stools are soft but the woman still finds difficulty in passing stools then a stimulant laxative should be considered.

Bulk-forming agents. Ispaghula, methylcellulose, sterculia and bran are typical bulk-forming agents and are usually taken as granules, powders or tablets. Their use is most appropriate in situations where dietary intake of fibre cannot be increased and the patient has small hard stools, haemorrhoids or an anal fissure.

The mechanism of action for bulk-forming agents involves polysaccharide and cellulose components that are not digested and which retain fluid, increase faecal bulk and stimulate peristalsis. They may also encourage the proliferation of colonic bacteria and this helps further increase faecal bulk and stool softness. Following ingestion it usually takes 12–36 h before any effect is seen but it may take longer. An adequate volume of fluid should also be ingested to avoid intestinal obstruction. Bulk-forming agents can be used safely long term, during pregnancy or breast feeding but many users will experience problems with flatulence and distension. The use of bulk-forming agents is not recommended in patients with colonic atony, intestinal obstruction or faecal impaction and they are less effective, or may even exacerbate constipation, in those who lack mobility.

Stimulant laxatives. Drugs in this group include bisacodyl, senna and dantron. They directly stimulate colonic nerves that cause movement of the faecal mass, reduce transit time and result in the passage of stool within 8–12 h. As a consequence of their time to onset, oral dosing at bedtime is generally recommended. For a rapid action (within 20–60 min), suppositories can be used. Abdominal cramps are common as an immediate side effect of stimulant laxatives, while electrolyte disturbances and an atonic colon may result from chronic use.

In the elderly, atonic colon is of less concern and prolonged use may be appropriate in a few cases. Stimulant laxatives should be avoided in patients with intestinal obstruction, and

Table 14.2 Examples of medicines known to cause constipation (frequency defined as very common [>10%] or common [1–10%])

α-Blocker	Prazosin
Antacid	Aluminium and calcium salts
Anticholinergic	Trihexyphenidyl, hyoscine, oxybutynin, procyclidine, tolterodine
Antidepressant	Tricyclics, SSRIs, reboxetine, venlafaxine, duloxetine, mirtazepine
Antiemetic	Palonosetron, dolasetron, aprepitant
Antiepileptic	Carbamazepine, oxcarbazepine
Antipsychotic	Phenothiazines, haloperidol, pimozide and atypical antipsychotics such as amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, zotepine, clozapine
Antiviral	Foscarnet
β-Blocker	Oxprenolol, bisoprolol, nebivolol; other β-blockers cause constipation more rarely
Bisphosphonate	Alendronic acid
CNS stimulant	Atomoxetine
Calcium channel blocker	Diltiazem, verapamil
Cytotoxic	Bortezomib, buserelin, cladribine, docetaxel, doxorubicin, exemestane, gemcitabine, irinotecan, mitozantrone, pentostatin, temozolomide, topotecan, vinblastine, vincristine, vindesine, vinorelbine
Dopaminergic	Amantadine, bromocriptine, carbegolide, entacapone, tolcapone, levodopa, pergolide, pramipexole, quinagolide
Growth hormone antagonist	Pegvisomant
Immunosuppressant	Basiliximab, mycophenolate, tacrolimus
Lipid-lowering agent	Colestyramine, colestipol, rosuvastatin, atorvastatin (other statins uncommon) gemfibrozil
Iron	Ferrous sulphate
Metabolic disorder	Miglustat
Muscle relaxant	Baclofen
NSAID	Meloxicam; other NSAIDs, for example, aceclofenac, and COX-2 inhibitors reported as uncommon
Smoking cessation	Bupropion
Opioid analgesic	All opioid analgesics and derivatives
Ulcer healing	All proton pump inhibitors, sucralfate

dantron alone, or in combination with a faecal softener, is restricted for use in constipation in terminally ill patients of all ages, because animal studies have demonstrated that it has carcinogenic and genotoxic properties.

Osmotic laxatives. Osmotic laxatives include magnesium salts, phosphate enemas, sodium citrate enemas, lactulose and macrogols. These agents retain fluid in the bowel by osmosis or change the water distribution in faeces to produce a softer, bulkier stool. Their ingestion should be accompanied by an appropriate fluid intake.

Rectal preparations of phosphates and sodium citrate are useful for quick relief, within 30 min, and bowel evacuation before abdominal radiological procedures, sigmoidoscopy and surgery. Oral magnesium salts such as the sulphate are also indicated for rapid bowel evacuation and have an effect within 2–5 h.

Lactulose is a semisynthetic disaccharide, which is not absorbed from the gut. It increases faecal weight, volume and bowel movement and must be taken regularly. It may take 48 h or longer to work. It is also useful in the treatment of hepatic

encephalopathy since it produces an osmotic diarrhoea of low faecal pH that discourages the growth of ammonia-producing organisms. Macrogols are inert polymers of ethylene oxide which induce a laxative effect by sequestering fluid in the bowel and like lactulose may take 48 h or more to exert an effect.

Faecal softeners/emollient laxatives. Docusate sodium is a non-ionic surfactant that has stool-softening properties. It reduces surface tension, increases the penetration of intestinal fluids into the faecal mass and has weak stimulant properties. Rectal docusate has a rapid onset of action but should not be used in individuals with haemorrhoids or anal fissure.

The classic lubricant, liquid paraffin, has no place in modern therapy. It seeps from the anus and is associated with granulomatous reactions following absorption of small quantities, lipoid pneumonia following aspiration and malabsorption of fat-soluble vitamins.

Diarrhoea

Diarrhoea is defined as the increased passage of loose or watery stools relative to the person's usual bowel habit. It may be accompanied by anorexia, nausea, vomiting, abdominal cramps or bloating. It is not a disease but a sign of an underlying problem such as an infection or gastro-intestinal disorder. The most likely cause of diarrhoea in all age groups is viral or bacterial infection; therefore, the following section primarily focuses on acute infective gastroenteritis but also includes reference to drug-induced diarrhoea. Diarrhoea can be associated with other conditions, for example, irritable bowel syndrome, inflammatory bowel disease, colorectal cancer and malabsorption syndromes, but these will not be covered here.

Acute gastroenteritis is most common in children but the precise incidence is not known because many cases are self-limiting and not reported. Nevertheless, diarrhoeal illness in children leads to high consultation rates with primary care doctors and accounts for one in five consultations in the 0–4 age group. It has been estimated that children under the age of 5 years have between one and three bouts of diarrhoea per year. Children in the same age range account for over 5% of consultations to primary care doctors, with 18,000 children a year in England and Wales being admitted to hospital with rotavirus infection.

The incidence of diarrhoea in adults is, on average, just under one episode per person each year. Many of these cases are thought to be food related, with 22% of those consulting a doctor claiming to have 'food poisoning'. Traveller's diarrhoea is another common cause of diarrhoea. For high-risk travel to areas such as Africa, Asia and South America, the reported incidence is more than 20%. Over recent years, *Escherichia coli* O157 has gained prominence because of a number of outbreaks in different communities associated with severe disease and even death. It is, however, an uncommon cause of diarrhoea, accounting for only 0.1% of all cases.

Aetiology

In the UK, rotavirus and small round structured virus (SRSV) are the most common identified causes of gastroenteritis in children. In adults, Campylobacter followed by rotavirus are the most common causes, although rates of norovirus have reported to be on the increase. Other identified causes include: the bacteria *E. coli*, Salmonella, Shigella, *Clostridium perfringens* enterotoxin; viruses such as adenovirus and astrovirus; and the protozoa Cryptosporidium, Giardia and Entamoeba. These pathogens produce diarrhoea via a number of methods: for example, enterotoxigenic *E. coli* produce enterotoxins that affect gut function with secretion and loss of fluids; by interfering with normal mucosal function, for example, adherent enteropathogenic *E. coli*; or by causing injury to the mucosa and deeper tissues, for example, enteroinvasive *E. coli* or enterohaemorrhagic *E. coli* such as *E. coli* O157. Other organisms, for example, *Staphylococcus aureus* and *Bacillus cereus*, produce preformed enterotoxins which on ingestion induce rapid-onset diarrhoea and vomiting that usually last less than 12 h.

So-called traveller's diarrhoea frequently affects people travelling from an area of more developed standards of hygiene to a less developed area. In many instances, the cause remains unknown, even after stool culture, but where a pathogen is identified, bacterial infection is responsible in over 80% of cases, and associated with ingestion of contaminated food or water and occurs during or shortly after travel. Bacterial pathogens commonly isolated include *E. coli*, Shigella, Salmonella, Campylobacter, Vibrio and Yersinia species. Viruses (10–15% of cases) and parasites (2–10% of cases), such as norovirus, Giardia, Cryptosporidium and Entamoeba, account for the remainder.

Many medicines, particularly broad-spectrum antibiotics such as ampicillin, erythromycin and neomycin, induce diarrhoea secondary to therapy (Table 14.3). With these antibiotics the mechanism involves the overgrowth of antibiotic-resistant bacteria and fungi in the large bowel after several days of therapy. The diarrhoea is generally self-limiting. However, when the overgrowth involves *Clostridium difficile* and the associated production of its bacterial toxin, life-threatening pseudomembranous colitis may be the outcome.

Signs and symptoms

Acute-onset diarrhoea is associated with loose or watery stools that may be accompanied by anorexia, nausea, vomiting, abdominal cramps, flatulence or bloating. When there is blood in the diarrhoea this is classed as dysentery and indicates the presence of an invasive organism such as Campylobacter, Salmonella, Shigella or *E. coli* O157.

The history of symptom onset is important. The duration of diarrhoea, whether other members of the family and contacts are ill, recent travel abroad, food eaten, antibiotic use and weight loss are all important factors to elucidate. The possibility of underlying diseases such as AIDS or infective proctitis in homosexual men must also be considered.

Dehydration is a common problem in the very young and frail elderly and the signs and symptoms must be recognised.

Table 14.3 Examples of medicines known to cause diarrhoea (defined as very common [>10%] or common [1–10%])

α-Blocker	Prazosin
ACE inhibitor	Lisinopril, perindopril
Angiotensin receptor blocker	Telmisartan
Acetylcholinesterase inhibitor	Donepezil, galantamine, rivastigmine
Antacid	Magnesium salts
Antibacterial	All
Antidiabetic	Metformin, acarbose
Antidepressant	SSRIs, clomipramine, venlafaxine
Antiemetic	Aprepitant, dolasetron
Antiepileptic	Carbamazepine, oxcarbagepine, tiagabine, zonisamide, pregabalin, levtiracetam
Antifungal	Caspofungin, fluconazole, flucytosine, nystatin (in large doses), terbinafine, voriconazole
Antimalarial	Mefloquine
Antiprotozoal	Metronidazole, sodium stibogluconate
Antipsychotic	Aripiprazole
Antiviral	Abacavir, emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir, efavirinez, ganciclovir, valganciclovir, adefovir, oseltamivir, ribavrin, fosamprenavir
β-Blocker	Bisoprolol, carvedilol, nebivolol
Bisphosphonate	Alendronic acid, disodium etidronate, ibandronic acid, risedronate, sodium clodronate, disodium pamidronate, tiludronic acid
Cytokine inhibitor	Adalimumab, infliximab
Cytotoxic	All classes of cytotoxics
Dopaminergic	Levodopa, entacapone
Growth hormone antagonist	Pegvisomant
Immunosuppressant	Ciclosporin, mycophenolate, leflunomide
NSAID	All
Ulcer healing	All proton pump inhibitors
Vaccine	Pediacel (5 vaccines in 1), haemophilus, meningococcal
Miscellaneous	Calcitonin, strontium ranelate, colchicine, dantrolene, olsalazine, anagrelide, nicotinic acid, pancreatin, eplerenone, acamprosate

In children, the severity of dehydration is most accurately determined in terms of weight loss as a percentage of body weight prior to the dehydrating episode. Unfortunately, in the clinical situation pre-illness weight is rarely known; therefore, clinical signs of dehydration must be assessed. National Institute for Health and Clinical Excellence (2009) has issued guidance on assessing the level of dehydration in children under 5 years of age and appropriate fluid management depending on the level of dehydration. Symptoms that could indicate mild dehydration are vague and include tiredness, anorexia, nausea and light-headedness.

Symptoms become more prominent in moderate dehydration and include dry mucous membranes, sunken eyes, decreased

skin turgor (pinch test of 1–2 s or longer), tachycardia, apathy, dizziness and postural hypotension. In severe dehydration, the above symptoms are more marked and may also include hypovolaemic shock, oliguria or anuria, cold extremities, a rapid and weak pulse and low or undetectable blood pressure.

Investigations

Before any investigations are undertaken a medication history is required to eliminate antibiotic- and other drug-induced diarrhoeas, or the possibility of a laxative overuse-induced diarrhoea. Testing for *C. difficile*-induced pseudomembranous colitis is indicated in those with severe symptoms or where hospitalisation or antibiotic therapy with lincomycins, broad-spectrum β-lactams or cephalosporins has occurred within the preceding 6 weeks.

In general, stool culture is required in patients who are immunocompromised, with bloody diarrhoea, severe symptoms, where there is no improvement within 48 h. Stool culture is also required when there is a history of recent overseas travel to non-Western countries.

Where the diarrhoea persists for more than 10 days, further investigation should be undertaken to exclude parasites such as Giardia, Entamoeba and Cryptosporidium. Acute, severe or persistent diarrhoea in a homosexual male or patient with AIDS warrants referral for specialist advice.

Treatment

Acute infective diarrhoea, including traveller's diarrhoea, is usually a self-limiting disorder. However, depending on the causative agent, a number of complications may have to be dealt with. Dehydration and electrolyte disturbance can be readily treated but may, if severe, progress to acidosis and circulatory failure with hypoperfusion of vital organs, renal failure and death. Toxic megacolon due to infective colitis has been documented; associated arthritis or Reiter's syndrome may complicate the invasive diarrhoeas of Campylobacter and Yersinia; Salmonella species may infiltrate bones, joints, meninges and the gallbladder; and *E. coli* infection may, for example, be complicated by haemolytic uraemic syndrome.

General measures

Patients should be advised on handwashing and other hygiene-related issues to prevent transmission to other family members. Promotion of handwashing has been shown to decrease diarrhoeal episodes by approximately one-third (Ejemot et al., 2008). Exclusion from work or school until the patient is free of diarrhoea is advised. In acute, self-limiting diarrhoea, children, healthcare workers and food handlers should be symptom free for 48 h before returning to school or work. More exacting criteria for return to work, such as testing for negative stool samples, are rarely required.

In both children and adults, normal feeding should be restarted as soon as possible. In weaned and non-weaned children with gastroenteritis, early feeding after rehydration has been shown to result in higher weight gain, no deterioration or prolongation of the diarrhoea and no increase in vomiting or lactose intolerance (Conway and Ireson, 1989, Sandhu et al., 1997). Similarly, breast-feeding infants should continue to feed throughout the rehydration and maintenance phases of therapy. Avoidance of milk or other lactose-containing food is seldom justified.

Dehydration treatment

Since diarrhoea results in fluid and electrolyte loss, it is important to ensure the affected individual maintains adequate fluid intake. Most patients can be advised to increase their intake of fluids, particularly fruit juices with their glucose and potassium content, and soups because of their sodium chloride content. High-carbohydrate foods such as bread and pasta can also be recommended because they promote glucose and sodium co-transport.

Young children and the frail elderly are prone to diarrhoea-induced dehydration and use of an oral rehydration solution (ORS) is recommended. The formula recommended by the World Health Organization (WHO) contains glucose, sodium, potassium, chloride and bicarbonate in an almost isotonic fluid. A number of similar preparations are available commercially in the form of sachets that require reconstitution in clean water before use (Table 14.4). Glucose concentrations between 80 and 120 mmol/L are needed to optimise sodium absorption in the small intestine. Glucose concentrations in excess of 160 mmol/L will cause an osmotic gradient that will result in increased fluid and electrolyte loss. High sodium solutions, in excess of 90 mmol/L, may lead to hypernatraemia, especially in children, and should be avoided. Until recently, the WHO ORS contained 90 mmol/L sodium, as cholera is more common in developing countries and associated with rapid loss of sodium and potassium. However, a systematic review of trials using a reduced osmolarity ORS (Hahn et al., 2002) concluded that solutions with a reduced

Table 14.4 Composition of oral rehydration solutions

	Osmolarity (mOsm/L)	Glucose (mmol/L)	Sodium (mmol/L)	Chloride (mmol/L)	Potassium (mmol/L)	Base (mmol/L)
Dioralyte®	240	90	60	60	20	Citrate 10
Electrolade®	251	111	50	40	20	Bicarbonate 30
WHO ORS	245	75	75	65	20	Citrate 10

osmolarity compared to the standard WHO formula were associated with fewer unscheduled intravenous infusions, a trend towards reduced stool output and less vomiting in children with mild-to-moderate diarrhoea. Based on this and other findings, the WHO ORS now has a reduced osmolarity of 245 mOsm/L and contains 75 mmol of sodium.

Commercially available solutions in the UK contain lower sodium concentrations as diarrhoea tends to be isotonic, and therefore replacement of large quantities of sodium is less important and indeed may be harmful. The presence of potassium prevents hypokalaemia occurring in the elderly, especially in those taking diuretics. ORS should be routinely used in both primary and secondary care settings. There appears to be no significant difference between intravenous and oral rehydration (Gavin et al., 1996).

For healthy adults, an appropriate substitute for a rehydration sachet is 1 level teaspoonful of table salt plus 1 tablespoon of sugar in 1 L of drinking water. The volume of ORS to be taken in treating mild-to-moderate diarrhoea is dependent on age. In adults, 2 L of oral rehydration fluid should be given in the first 24 h, followed by unrestricted normal fluids with 200 mL of rehydration solution per loose stool or vomit. For children, 30–50 mL/kg of an ORS should be given over 3–4 h. This can be followed with unrestricted fluids, either with normal fluids alternating with ORS or normal fluids with 10 mL/kg rehydration solution after each loose stool or vomit (Murphy, 1998). The solution is best sipped every 5–10 min rather than drunk in large quantities less frequently.

Care is required in diabetic patients who may need to monitor blood glucose levels more carefully.

Drug treatment

Antimotility agents. In acute diarrhoea, antimotility agents such as loperamide, diphenoxylate and codeine are occasionally useful for symptomatic control in adults who have mild-to-moderate diarrhoea and require relief from associated abdominal cramps. Antimotility agents are not recommended for use in children as trial results appear contradictory and any benefits are small with unacceptable levels of side effects observed. Management should initially focus on prevention or treatment of fluid and electrolyte depletion before antimotility agents are considered.

Antimotility agents should be avoided in severe gastroenteritis or dysentery because of the possibility of precipitating ileus or toxic megacolon. All appear to have comparable efficacy but loperamide is the drug of choice given its low incidence of CNS effects.

Diphenoxylate. Diphenoxylate is a synthetic opioid available as co-phenotrope in combination with a subtherapeutic dose of atropine. The atropine is present to discourage abuse but may cause atropinic effects in susceptible individuals. Administration of co-phenotrope at the recommended dosage carries minimal risk of dependence. However, prolonged use or administration of high doses may produce a morphine-type dependence. Its adverse effect profile resembles that of morphine.

In cases of suspected overdose, signs may be delayed for up to 48 h. Young children are particularly susceptible to diphenoxylate overdose where as few as 10 tablets of co-phenotrope may be fatal.

Concurrent use of diphenoxylate with monoamine oxidase inhibitors can precipitate a hypertensive crisis, while the action of CNS depressants such as barbiturates, tranquillisers and alcohol is enhanced.

Loperamide. Loperamide is a synthetic opioid analogue that exerts its action by binding to opiate receptors in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time, enhancing the resorption of water and electrolytes, reducing gut secretions and increasing anal sphincter tone. In uncomplicated diarrhoea, it may have an effect within 1 h of oral administration. It is relatively free of CNS effects at therapeutic doses, although CNS depression may be seen in overdose, particularly in children. As it undergoes hepatic metabolism it should be used with caution in patients with hepatic dysfunction.

Codeine and morphine. The constipating side effect of the opioid analgesics codeine and morphine may be used to treat diarrhoea. Both are susceptible to misuse and, given in large doses, may induce tolerance and psychological and physical dependence. Morphine may still be obtained in combination with agents such as the adsorbent kaolin, for example, kaolin and morphine. However, it has no evidence of efficacy in the treatment of diarrhoea and should not be recommended.

Bismuth subsalicylate. Bismuth subsalicylate is an insoluble complex of trivalent bismuth and salicylate that has been shown to be effective in reducing stool frequency. It possesses antimicrobial activity on the basis of its bismuth content while the salicylate is considered to confer antisecretory properties. At therapeutic doses it is relatively free from side effects, although it may cause blackening of the tongue and stool. The relatively large quantity of the liquid preparation that has to be consumed is seen as a disadvantage.

Antimicrobials. Antibiotics are generally not recommended in diarrhoea associated with acute infective gastroenteritis. Inappropriate use will only contribute further to the problem of resistant organisms. There is, however, a place for antibiotics in patients with positive stool culture where the symptoms are not receding or for travellers' diarrhoea (De Bruyn et al., 2000). In patients presenting with dysentery or suspected exposure to bacterial infection, treatment with a quinolone, for example, ciprofloxacin, may be appropriate. However, quinolones are not without their problems: they may cause tendon damage or induce convulsions in epileptics, in situations that predispose to seizures, and in patients taking NSAIDs. Their use in adolescents is also not recommended because of an association with arthropathy.

Where Campylobacter is the suspect causative organism, patients with severe symptoms or dysentery should receive early treatment with erythromycin or ciprofloxacin. Severe symptoms or dysentery associated with Shigella can also be treated with ciprofloxacin. Nalidixic acid can be used in children and trimethoprim may be appropriate in pregnant women where resistance is not a problem.

The use of antibiotics in patients with Salmonella is not generally recommended because of the likelihood that excretion

is prolonged. Antibiotics may, however, be indicated in the very young and the immunocompromised. The benefit of antibiotic use in enterohaemorrhagic infection, for example, *E. coli* O157, is less clear. In this situation, there is evidence that antibiotics cause toxins to be released which may lead to haemolytic uraemic syndrome.

In both amoebic dysentery and giardiasis, metronidazole is the drug of choice. Diloxanide is also used in amoebic dysentery to ensure eradication of the intestinal disease. Antibiotics are not indicated in the treatment of cryptosporidiosis in immunocompromised individuals.

Probiotics. Probiotics have been defined as components of microbial cells or microbial cell preparations that have a beneficial effect on health. Well-known probiotics include lactic acid bacteria and the yeast Saccharomyces. The rationale for their use in infectious diarrhoea is that they act against enteric pathogens by competing for available nutrients and binding sites, making gut contents acid and increasing immune responses. A Cochrane review (Allen et al., 2003) concluded that whilst probiotics in individual studies appeared moderately effective as adjunctive therapy, there were insufficient studies of specific probiotic regimens to inform the development of evidence-based treatment guidelines.

Zinc. The use of zinc has been reviewed in the treatment of diarrhoea in children in developing countries (Lazzerini et al., 2008). In this context, zinc has been shown to be of value in children older than 6 months, probably because they have some prior, underlying deficiency of zinc.

Rotavirus vaccine. Rotavirus vaccine has been shown to protect against the most common strains of rotavirus (G1 and G3), although the benefits of the vaccine are dependant on the type of vaccine used, with rhesus and human rotavirus the most efficacious (Soares-Weiser, 2004).

Some of the common therapeutic problems in the management of individuals with constipation and diarrhoea are outlined in Table 14.5.

Table 14.5 Common therapeutic problems in constipation and diarrhoea

Problem	Comment
Constipation	
Bulk laxative, for example ispaghula, taken at bedtime	Drugs such as ispaghula should not be taken before going to bed because of risk of oesophageal blockage
Urine changes colour	Anthraquinone glycosides, for example senna, are excreted by the kidney and may colour urine yellowish-brown to red colour, depending on pH
Patient claims dietary and fluid advice ineffective in resolving constipation	May find high-fibre diet difficult to adhere to, socially unacceptable, and expect result in less than 4 weeks
Patient taking docusate complains of unpleasant aftertaste or burning sensation	Advise to take with plenty of fluid after ingestion
Sterculia as Normacol® and Normacol Plus® granules or sachets	The granules should be placed dry on the tongue and swallowed immediately with plenty of water or a cool drink. They can also be sprinkled onto and taken with soft food such as yoghurt
Methylcellulose (Celevac®)	Each tablet should be taken with at least 300 mL of liquid
Diarrhoea	
Antimotility agent requested for a young child	Antimotility agents must be avoided in young children or patients with severe gastroenteritis or dysentery
Antimotility agent requested by patient with persistent diarrhoea (>10 days)	Antimotility agent inappropriate. Stool culture required to exclude parasitic infection such as Giardia, Entamoeba and Cryptosporidium
Adult with diarrhoea stops eating and drinking to allow diarrhoea to settle	Patient should eat and drink as normally as possible. Plenty of fluids required to prevent dehydration. Fruit juice (glucose and potassium), soup (salt), bread and pasta (carbohydrate) are of particular benefit
Reconstitution of oral rehydration solution	Each sachet of Diorolyte® and Electrolade® requires 200 mL of water. They should be discarded after 1 h after preparation unless stored in a fridge when they may be kept for 24 h

Case studies

Case 14.1

Mr J, a man in his 30s, asks to speak to the pharmacist. He has constipation and has taken some medicine, lactulose, but he is still finding it difficult to go to the toilet. He asks for a stronger laxative.

Question

What further information do you need to obtain to be in a position to help Mr J?

Answer

Constipation is rarely a symptom of sinister pathology in someone of Mr J's age. The most likely cause is a diet low in fibre and inadequate fluid intake. Establish the duration and nature of the problem and discuss with Mr J his usual diet. Determine if there has been any change to his diet recently, which may have precipitated the constipation. Social factors also play a role in constipation, so it is prudent to ask if there have been any life changes such as a loss of job or difficulties with family life. If his replies to the questions raise no suspicion of underlying medical problems then dietary advice only may be needed. However, since he has already taken lactulose it is likely he will persist in his request for a suitable laxative. Question Mr J on how he took the lactulose and for how long. Patients often have misconceptions on how quickly a medicine will work. A stimulant laxative may be a suitable alternative for Mr J as it has a quicker onset of action.

Case 14.2

Mr A's mother has recently moved in with his family following the death of his father 4 months ago. Although she was formerly a sprightly 78 year old, she is now withdrawn, eats little of the meals prepared for her and no longer goes for her daily walks. Mr A knows she is taking medicine for a long-standing heart complaint and has recently started taking antidepressants. She is complaining of constipation.

Question

Mr A would like to know if there is any medicine suitable to help his mother.

Answer

Constipation is a common problem in the elderly. Activity levels often diminish and many also suffer from medicine-induced constipation exacerbated by reduced muscle tone. Pain on defaecation associated with haemorrhoids is also a common contributory factor. The elderly often have poor dental status or false teeth and consequently avoid high-fibre foods because they are more difficult to chew.

In the case of Mr A's mother, the history provides little insight into the duration of the problem, although there are a number of factors that warrant further investigation. Clearly, a reduction in physical activity has occurred and her diet and fluid intake may have changed. The death of her husband and loss of independence are significant lifestyle issues for Mr A's mother that cannot readily be addressed and probably account for the recent introduction of antidepressants. The identity of her 'heart medicine' may reveal a drug-induced factor that could have been enhanced by the recent prescription for antidepressants. It is also unclear whether she has been constipated previously.

Appropriate exercise, proper diet and sufficient fluid may be the only key actions that need to be taken.

Case 14.3

Mr B is a busy 45-year-old executive who works for a large multinational company. He has noted blood in his stools over the past 2 weeks and for 3 days has had continuous abdominal discomfort. He has discussed his symptoms with his wife and they suspect haemorrhoids are the cause. Mr B is going away on business in 6 days and seeks your advice on a suitable treatment.

Question

What advice should be given to Mr B?

Answer

Blood in the stool is not necessarily serious. If the blood appears fresh and can only be seen on the surface of the stool it is likely the source is the anus or distal colon. It is probably caused by straining and bleeding from haemorrhoids or an anal fissure. Similarly, if the blood appears as specks or as a smear on the toilet paper after defaecation, this is also likely to indicate haemorrhoids, particularly if such a diagnosis has been made previously following clinical examination.

If the blood is mixed with the faeces and has a dark or 'tarry' appearance then a more serious underlying cause is possible. The darker the faeces, the more suggestive they are that there has been an upper GI bleed or a substantial loss of blood from the large bowel. If this is the case the patient should have a proper clinical examination.

Iron or bismuth tablets can cause darkened stools, so it is important to take a medication history from the patient.

However, given Mr B's age, recent onset of symptoms and the presence of continuous abdominal pain accompanying the constipation, a thorough clinical examination is required to eliminate sinister pathology such as bowel obstruction caused by a tumour or diverticular disease.

Case 14.4

A 7-year-old boy in previous good health was admitted to hospital with bloody diarrhoea and dehydration 4 days after attending a children's birthday party. He was treated with intravenous fluids and given nothing by mouth. The day after admission to hospital a colonoscopy revealed haemorrhagic colitis. His diarrhoea seemed to be improving up to day 5 when he experienced a generalised convulsion following which he was transferred to a children's intensive care bed. He was irritable, pale and hypertensive, and an emergency laboratory report revealed thrombocytopenia, hyponatraemia and hyperkalaemia.

Questions

1. What is the likely diagnosis in this child?
2. What specific therapy is required?

Answers

1. This patient probably has haemolytic uraemic syndrome caused by *E. coli* O157. Haemolytic uraemic syndrome is the most common form of acquired renal insufficiency in young children. It is characterised by nephropathy, thrombocytopenia and microangiopathic haemolytic anaemia. Although there are a number of potential causative factors, the most common is the toxin-producing O157 strain of *E. coli*. In 1996, 21 people died from *E. coli* O157 after eating contaminated meat from a butcher's shop in Scotland. In 2001, 13 Girl Guides and their leader contracted *E. coli* O157 after camping in a field in Inverclyde, Scotland, previously grazed by sheep and in 2005 more than 158 children from 42 schools in South Wales were affected by eating contaminated meat, one of whom died.

   The syndrome typically has a pro-drome of bloody diarrhoea occurring 5–7 days before onset of renal insufficiency. Colonoscopy is usually non-specific and shows haemorrhagic colitis. At diagnosis most children are pale and very irritable. Hypertension and hyponatraemia may be associated with convulsions and are generally a consequence of a disorder of fluid and salt balance. Laboratory findings may include anaemia and thrombocytopenia, hyponatraemia, hyperkalaemia, hypocalcaemia and metabolic acidosis. The kidney typically shows signs of glomerular endothelial injury. Capillary thrombosis is quite prominent but with no evidence of immune complex deposition. Similar findings can usually be seen in all other organs including the brain, liver and intestine.
2. Treatment is usually supportive. Fluid and electrolyte balance need to be corrected and the hypertension controlled. In cases with prolonged oliguria or anuria, peritoneal dialysis may be used. Approximately 85% of patients recover normal renal function.

Case 14.5

Mr G is planning to travel to Mexico on business. He was last there 6 months ago but was incapacitated with diarrhoea for 3 of 6 days in a busy work schedule. He does not want a repeat experience on his forthcoming visit and seeks advice about taking a course of antibiotics with him to use as empirical treatment should the need arise.

Questions

1. Is there any evidence that antibiotics are of benefit in traveller's diarrhoea?
2. Are there any problems associated with empirical use of antibiotics in traveller's diarrhoea?

Answers

1. The empirical use of antibiotics has been shown to increase the cure rate in individuals suffering from traveller's diarrhoea. Studies in travellers including students, package tourists, military personnel and volunteers have compared antibiotic use against placebo (De Bruyn et al., 2000). The antibiotics studied have included aztreonam, ciprofloxacin, co-trimoxazole, norfloxacin, ofloxacin and trimethoprim given for durations varying from a single dose to a 5-day treatment course. Overall, antibiotics increased the cure rate at 72 h (defined as cessation of unformed stools or less than one unformed stool/24 h) without additional symptoms.
2. The use of antibiotics in the treatment of traveller's diarrhoea does have problems. Adverse effects in up to 18% of recipients have been reported with gastro-intestinal (cramp, nausea, anorexia), dermatological (rash) and respiratory (cough, sore throat) symptoms the most frequently reported. Antibiotic-resistant isolates have also been reported following the use of ciprofloxacin, co-trimoxazole and norfloxacin. In the USA but not the UK, rifaximin, a semi-synthetic rifamycin derivative that is little absorbed from the gastro-intestinal tract, is licensed for the treatment of traveller's diarrhoea.

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15 Adverse effects of drugs on the liver

B. E. Featherstone

Key points

- Approximately 20–30% of acute liver failure cases are attributed to drugs.
- Risk of drug-induced liver disorders increases with age and is generally more common in women.
- Generally, drug-induced liver damage is either dose-related or idiosyncratic.
- Drugs can cause all types of liver disorder and should always be considered in patients presenting with liver-related problems.
- The clinical features of drug-induced hepatotoxicity vary widely, depending upon the type of liver damage caused.
- Treatment of drug-induced hepatotoxicity relies on correct diagnosis, prompt withdrawal of the causative agent and supportive therapy.
- Patients given potentially hepatotoxic drugs should be monitored regularly and taught how to recognise signs of liver dysfunction and advised to report symptoms immediately.
- Drugs causing dose-related hepatic toxicity may do so at lower doses in patients with liver disease than in patients with normal liver function and idiosyncratic reactions may occur more frequently in patients with existing liver disease.
- Any new drug has the potential to cause hepatotoxicity. Post-marketing surveillance is important to highlight new potential hepatotoxic effects.

An adverse drug reaction (ADR) is an effect that is unintentional, noxious and occurs at doses used for diagnosis, prophylaxis and treatment. A hepatic drug reaction is an ADR which predominantly affects the liver.

Drugs can induce almost all forms of acute or chronic liver disease, with some drugs producing more than one type of hepatic reaction. Although not a particularly common form of ADR, drugs should always be considered as a possible cause of liver disease.

Epidemiology

The incidence of drug-induced liver disease (DILD) has continued to rise steadily since the late 1960s, although the incidence of idiosyncratic reactions for most drugs remains low, occurring at therapeutic doses from 1 in every 1000 patients to 1 in every 100,000 patients. DILD is not usually life-threatening; however, for the small number of patients who develop drug-induced acute liver failure (ALF) the prognosis is poor, with a 60–80% mortality rate, unless they receive a liver transplant. The incidence and severity of DILD is shown in Fig. 15.1. It is estimated that 15–40% of ALF cases may be attributable to drugs. Classification of ALF suggests three classes: hyperacute, acute and subacute (Table 15.1).

In the early 1990s, acute overdose with paracetamol accounted for 30,000–40,000 hospital admissions and over half the cases of ALF referred to liver units. It is the definite cause of approximately 100 deaths a year in the UK. ALF induced by paracetamol has become an important indication for liver transplantation. Hepatotoxicity induced by such drugs as halothane, the antituberculous agents (isoniazid and rifampicin), psychotropics, antibiotics and cytotoxic drugs still continue to cause concern.

Many drugs cause elevated liver enzymes with apparently no clinically significant adverse effect, although in a few patients there may be significant hepatotoxicity. For example, isoniazid

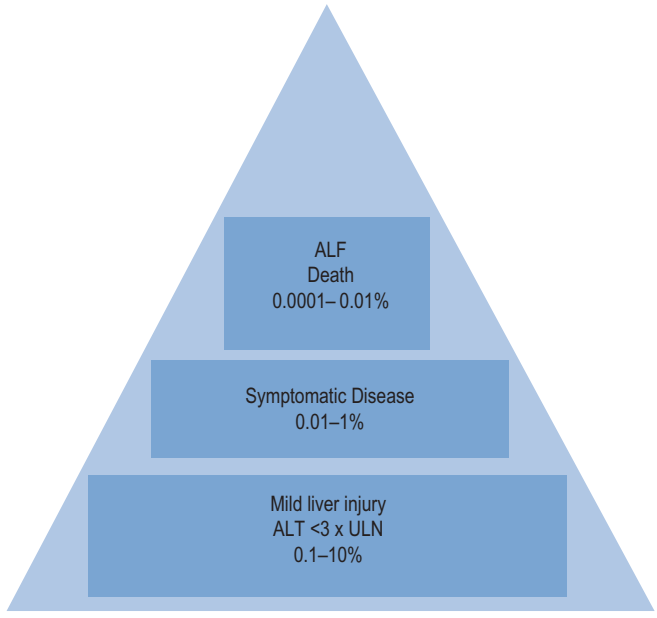


Fig. 15.1 The spectrum of drug-induced liver disease. ALF, acute liver failure; ALT, alanine transferase; ULN, upper limit of normal; % incidence of population taking medication.

Table 15.1 Characteristics of the different types of acute liver failure (Richardson and O'Grady, 2002)

Characteristic	Hyperacute	Acute	Subacute
Transition time from jaundice to encephalopathy	0–7 days	8–28 days	29–84 days
Cerebral oedema	Common	Common	Rare
Renal failure	Early	Late	Late
Ascites	Rare	Rare	Common
Coagulation disorder	Marked	Marked	Modest
Prognosis	Moderate	Poor	Poor

causes elevated liver enzymes in 10–36% of patients taking the drug as a single agent. However, only 1% suffer significant hepatotoxicity, with the liver function tests (LFTs) of the majority returning to normal if therapy is discontinued. Other examples of drugs that elevate liver enzymes are shown in Table 15.2.

Although it is not possible to identify patients who will suffer ADRs manifesting in hepatic toxicity, a number of risk factors have been identified.

Risk factors

Pre-existing liver disease

Pre-existing liver disease may increase the risk of developing drug-induced hepatic injury with agents such as methotrexate, cytotoxic agents, aspirin and sodium valproate. In general, patients with liver disease are more likely to suffer ADRs. A past medical history of DILD from any medication has been shown to be a predictor of future DILD from other drugs.

Age

It is generally accepted that the elderly are at an increased risk of ADRs. There are multiple reasons for this, including higher exposure rates and decreased metabolism. Drug-induced hepatic injury is more likely to occur in elderly patients than in those under 35 years of age. Similarly, halothane hepatitis and isoniazid or chlorpromazine hepatotoxicity are more likely in patients over 40 years of age. The severity of the reactions also appears to increase with age, especially in those over 60 years. Sodium valproate toxicity, on the other hand, demonstrates an increased risk of developing serious or fatal hepatotoxicity in those under 3 years, with risk decreasing as age advances. Aspirin is an example of another drug causing hepatotoxicity, specifically in children. Reye's syndrome in children has been linked to the use of aspirin following a viral illness; it is life-threatening and associated with coma, seizures and liver failure. A cholestatic presentation of DILD is more common in older patients and hepatocellular damage is generally more common in younger patients.

Table 15.2 Examples of drugs that elevate liver enzymes

Drug	Percentage of patients with increase in transaminases
Cefaclor	11%
Cefixime	0.7%
Ciprofloxacin	5%
Chlorpromazine	50%
Diclofenac	15%
Donepezil	MHRA reports[a]
Efavirenz	4%
Heparin/LWMH	5%
Isoniazid	10–36%
Naproxen	4%
Norfloxacin	0.1%
Nevirapine	12%
Niacin	50%
Rifampicin	15–30%
Sodium valproate	11%
SSRIs	MHRA reports[a]
Statins	1–2%
Sulphonamides	10%

[a]Available at: http://www.mhra.gov.uk

Gender

The frequency of drug-induced hepatotoxicity is thought to be more common in females than males, particularly with halothane, isoniazid, flucloxacillin, chlorpromazine, erythromycin and nitrofurantoin. However, evidence from a recent series of more than 600 cases of DILD found that female gender was not a risk factor. There is weak evidence of a gender difference in toxicity of sodium valproate, being more common in boys before puberty and in females after puberty. Cholestatic jaundice associated with co-amoxiclav has been reported to be more common in males than females.

Genetics

Genetic differences that affect an individual's ability to metabolise certain drugs may predispose to DILD. For example, both fast and slow acetylators may be more susceptible to isoniazid-induced liver damage. The conventional view is that rapid acetylators are at risk of increased toxic reactions due to transformation of acetylhydrazine by cytochrome P450 into a reactive metabolite; other studies suggest slow acetylation may result in toxicity due to formation of hydrazine, which is toxic in itself. When starting, isoniazid monitoring of LFTs is recommended monthly for the first 3 months, as toxicity is most likely to occur early in therapy.

Halothane-induced injury has been reported for multiple family members.

It is thought that a genetic predisposition to allergic forms of drug hypersensitivity could be a factor in some types of liver disease. Flucloxacillin liver injury has been associated with the human leukocyte antigen B*5701. Having this HLA haptotype confers an 80-fold increase in susceptibility to liver injury with flucloxacillin.

Enzyme induction

Alcohol, rifampicin and other drugs that induce cytochrome P450 isoenzyme 2El potentiate the risk of hepatotoxicity with other drugs such as paracetamol, isoniazid and halothane. The role of alcohol as a risk factor for DILD is, however, not clear-cut and acute and chronic alcohol consumption may have different effects.

Concomitant therapy with other anticonvulsants, particularly phenytoin and phenobarbital, is a risk factor for toxicity with sodium valproate, where 90% of cases of liver injury are associated with combination therapy.

Polypharmacy

A typical example of this is seen with NSAIDs. The risk of liver disease with NSAIDs is normally extremely low but is increased when NSAIDs are used with other hepatotoxic drugs.

Concurrent diseases and pregnancy

Pre-existing renal disease, diabetes, pregnancy and poor nutrition may all affect the ability of the liver to metabolise drugs effectively and may put the patient at risk of developing liver damage. Table 15.3 summarises the host factors that may predispose a patient to drug hepatotoxicity.

Aetiology

Drug-induced hepatotoxicity may present as an acute insult that may or may not progress to chronic disease, or it can present as an insidious development of chronic disease. The type of lesion may be cytotoxic (cellular destruction) or cholestatic (impaired bile flow). Cytotoxic damage may be further classified as necrotic (cell death) or steatic (fatty degeneration). The liver damage resulting from drug toxicity often presents as a mixed picture of cytotoxic and cholestatic injury.

Table 15.3 Examples of host factors that predispose to drug hepatotoxicity

Host factor	Drug example
Pre-existing liver disease	Methotrexate, aspirin, sodium valproate
Age	
Older	Halothane, isoniazid, chlorpromazine, co-amoxiclav, nitrofuratoin
Younger	Aspirin, sodium valproate
Gender	
Female	Halothane, isoniazid, nitrofurantoin, flucloxacillin, chlorpromazine, erythromycin
Male	Sodium valproate (in prepubescent boys), co-amoxiclav
Genetics	Halothane, chlorpromazine, phenytoin, carbamazepine, phenobarbital, paracetamol, flucloxacillin
Enzyme induction	Paracetamol, halothane, isoniazid, sodium valproate
Polypharmacy	NSAIDs if used with other hepatotoxic drugs Isoniazid with rifampicin or pyrazinamide Sodium valproate with phenytoin Paracetamol with zidovudine
Concurrent diseases	
Diabetes mellitus	Methotrexate
Renal failure	Allopurinol, i.v. tetracycline
Malnutrition	Paracetamol
HIV positive with hepatitis C or B co-infection	Antiretroviral agents

Table 15.4 Characteristics of intrinsic and idiosyncratic hepatotoxic reactions

	Intrinsic toxicity	Idiosyncratic toxicity	
Mechanism	Direct toxicity	Metabolic abnormality	Hypersensitivity reaction
dose-dependent	Yes	No	No
Predictable	Yes	No	No
Latency	Hours	Weeks to months	1–5 weeks
Type of injury	Usually necrosis	Any	Any
Clinical features	Acute liver failure	Increased liver enzymes, hepatitis, jaundice	Fever, rash, eosinophilia, arthralgias, hepatitis

The mechanisms of drug-induced hepatic damage can be divided into intrinsic (type A) and idiosyncratic (type B) hepatotoxicity (Table 15.4). Intrinsic hepatotoxicity is predictable, dose-dependent and usually has a short latency period ranging from hours to weeks. The majority of individuals who take a toxic dose are affected and exhibit the same type of injury. Examples are paracetamol, salicylates, methotrexate and tetracycline. Other examples are presented in Table 15.5. Toxicity may be avoided by ensuring the doses listed are not exceeded.

Idiosyncratic reactions occur at a low frequency, typically less than 1 in 100 individuals who are exposed to the drug. The latency period is variable, ranging from 5 to 90 days from the initial ingestion of the drug. The type of injury is less predictable and not dose-related. This type of reaction may be due to either drug hypersensitivity or a metabolic abnormality. Examples of drugs that induce idiosyncratic reactions are chlorpromazine, halothane and isoniazid.

The precise mechanisms resulting in DILD are often not completely understood, although injury to the hepatocytes may result directly from interference with intracellular function, membrane integrity or indirectly by immune-mediated damage to cells.

Table 15.5 Examples of dose-related drug-induced hepatotoxicity

Drug	Toxic dose
Paracetamol	Single dose >10 g
Tetracycline	>2 g daily (oral), increased risk of toxicity in pregnancy and renal failure
Methotrexate	Weekly dose >15 mg Cumulative dose >2 g in 3 years, increased risk of toxicity in pre-existing liver disease, alcohol abuse, diabetes
6-Mercaptopurine	>2.5 mg/kg
Vitamin A	Chronic use of 40,000 units daily
Cyclophosphamide	Daily dose >400 mg/m^2
Salicylates	Chronic use >2 g daily
Anabolic steroids	High dose >1 month
Oral contraceptive	Increased risk with higher oestrogen content, older preparations Duration of treatment
Iron	Single dose >1 g

Necrosis

Necrosis is characterised by cytotoxic cellular breakdown (hepatocellular destruction) and is generally associated with a poor prognosis. Drugs commonly associated with DILD have a variable propensity to cause hepatic necrosis. For example, hepatic necrosis has been reported in 3% of cases with co-amoxiclav DILD compared to 89% in individuals with halothane-induced liver injury cases.

Paracetamol causes hepatic necrosis when its normal metabolic pathway is saturated. Subsequent metabolism occurs by an alternative pathway that produces a toxic metabolite which covalently binds to liver cell proteins and causes necrosis.

Steatosis

In steatosis, hepatocytes become filled with small droplets of lipid (microvesicular fatty liver) or occasionally with lipid droplets that are much larger (macrovesicular fatty liver). Tetracyclines are thought to cause steatosis by interfering with synthesis of lipoproteins that normally remove triglycerides from the liver.

Cholestasis

Some drugs injure bile ducts and cause partial or complete obstruction of the common bile duct, resulting in retention of bile acids and the condition known as cholestasis. Cholestasis caused by anabolic and contraceptive steroids is due to inhibition of bilirubin excretion from the hepatocyte into the bile.

The penicillins, although commonly associated with allergic drug reactions, are a very rare cause of liver disease. The

isoxazoyl group present in the synthetic β-lactamase resistant oxypenicillins has been implicated as a cause of liver injury. Acute cholestatic hepatitis has increasingly been reported during treatment with flucloxacillin, and in some countries this has become the most important cause of drug-induced cholestatic hepatitis. The incidence appears to be about twice that of the related isoxazoyl penicillins cloxacillin and dicloxacillin. Moreover, there is likely to be underreporting due to a delay in onset of up to 42 days after stopping treatment. Female sex, age over 55 years, longer courses and high daily doses also seem to be associated with a higher risk of liver reaction to flucloxacillin.

Rifampicin causes hyperbilirubinaemia by inhibiting uptake of bilirubin by the hepatocyte as well as inhibiting bilirubin excretion into bile. This is generally not an indication for interrupting rifampicin therapy, although liver function will need to be closely monitored. Other therapeutic agents affect sinusoidal or endothelial cells, which may result in veno-occlusive disease or fibrosis. Vitamin A affects the fat storing cells, causing toxicity that leads to fibrosis.

Pathophysiology

The range of DILDs is illustrated in Table 15.6. Increased serum level of hepatobiliary enzymes without clinical liver disease occurs with variable frequency between drugs but for some agents it may occur in up to half the patients who receive a drug. This may reflect subclinical liver injury.

Hepatocellular necrosis

In severe cases, acute hepatocellular necrosis presents with jaundice and LFT abnormalities, including a modestly raised alkaline phosphatase and a markedly elevated alanine aminotransferase level of up to 200 times the upper limit of the reference range. Prolongation of the prothrombin time occurs but depends on the severity of the injury, increasing dramatically in severe cases. Microscopy reveals necrosis of the hepatocytes in a characteristic pattern.

Steatosis

Steatosis (fatty liver) is the accumulation of fat droplets within liver cells and is associated with abnormal LFTs, although the elevation of alanine aminotransferase is not as high as that seen in acute hepatocellular necrosis. Hyperammonia, hypoglycaemia, acidosis and clotting factor deficiency may also be present. Histologically, the liver damage resembles the acute fatty liver of pregnancy. Fat distribution within the hepatocyte is either microvesicular, as occurs with tetracycline, aspirin and sodium valproate, or macrovesicular where the hepatocyte cell nucleus is displaced to the periphery by a single large fat droplet. This type of damage occurs typically with steroids, methotrexate, alcohol and amiodarone.

A less severe, more chronic form of fatty liver, steatohepatitis, also occurs. Steatohepatitis differs from diffuse fatty

Table 15.6 Examples of adverse drug reactions on the liver

Adverse reaction	Drugs associated with reaction
Hepatocellular necrosis	Paracetamol Propylthiouracil Salicylates Iron salts Allopurinol Dantrolene Halothane Ketoconazole Isoniazid Mithramycin Cocaine 'Ecstasy' (methylenedioxymetamphetamine, MDMA)
Fatty liver	Amiodarone Tetracyclines Steroids Sodium valproate L-Asparaginase
Cholestasis	Oral contraceptives Carbimazole Anabolic steroids Ciclosporin
Cholestasis with hepatitis	Chlorpromazine Tricyclic antidepressants Erythromycin Flucloxacillin Co-amoxiclav ACE inhibitors Sulphonamides Sulphonylureas Phenytoin NSAIDs Cimetidine Ranitidine Trazodone
Granulomatous hepatitis	Phenytoin Allopurinol Carbamazepine Clofibrate Hydralazine Sulphonamides Sulphonylureas
Acute hepatitis	Dantrolene Isoniazid Phenytoin
Chronic active hepatitis	Methyldopa Nitrofurantoin Isoniazid
Fibrosis and cirrhosis	Methotrexate Methyldopa Vitamin A (dose-related)
Vascular disorders	Azathioprine Dactinomycin Dacarbazine

change. Notably, the clinical symptoms and biochemistry resemble chronic parenchymal disease and the histology is similar to that seen in alcoholic hepatitis. Amiodarone is an example of a drug that can cause chronic steatohepatitis associated with phospholipidosis.

Cholestasis

Cholestasis without hepatitis is associated with a raised bilirubin and a normal or minimally raised alanine aminotransferase level. No inflammation or hepatocellular necrosis is seen. In contrast, cholestasis associated with hepatitis presents with raised bilirubin, alanine aminotransferase and alkaline phosphatase levels and a certain amount of liver damage.

Granulomatous hepatitis

Granulomatous hepatitis occurs with modestly elevated LFTs and, usually, normal synthetic liver function. Histology reveals granulomas and tissue eosinophilia.

Acute hepatitis

Acute hepatitis resembles viral hepatitis with LFTs raised in proportion to the severity of the hepatocellular damage. The best indicator of severity is the prothrombin time. Histologically, necrosis and cellular degeneration are seen in combination with an inflammatory infiltrate.

Chronic active hepatitis

Chronic active hepatitis may present as an acute injury or progress to cirrhosis. Serum transaminases are usually raised and albumin is low. The histology resembles that of autoimmune chronic active hepatitis and is associated with circulating autoantibodies. Methyldopa is an example of a drug that can cause chronic active hepatitis.

Fibrosis

In patients with fibrosis, the serum transaminase levels may be only slightly raised, and are not good predictors of hepatic damage. Microscopy shows deposition of fibrous tissues. Fibrosis may proceed to cirrhosis. Such damage may be seen with long-term methotrexate use.

Vascular disorders

A variety of drugs can cause veno-occlusive disease, which is characterised by non-thrombotic narrowing of small centrilobular veins, and is typically caused by cytotoxic agents and some herbal remedies. Use of oral contraceptives or cytotoxic agents may exacerbate an underlying thrombotic disorder and increase the risk of the Budd–Chiari syndrome (obstruction of the large veins) developing.

Tumours

Drugs have been associated with a variety of hepatic tumours. The drugs most commonly linked to malignancy are the oral contraceptives, anabolic steroids and danazol.

Clinical manifestations

The clinical features of drug-induced hepatotoxicity vary widely, depending on the type of liver damage caused.

Acute hepatocellular necrosis

In acute hepatocellular necrosis caused by paracetamol, early symptoms include anorexia, nausea and vomiting, malaise and lethargy. Abdominal pain may be the first indication of liver damage but is not usually apparent for 24–48 h. A period of apparent recovery precedes the development of jaundice and production of dark urine. If the liver injury is severe, deterioration follows, with repeated vomiting, hypoglycaemia, metabolic acidosis, bruising and bleeding, drowsiness and hepatic encephalopathy. Oliguria (diminished urine output) and anuria (complete cessation of urine production) may result from acute tubular necrosis. Renal failure may occur even in the absence of severe liver disease. In addition to acute renal failure, myocardial injury and pancreatitis have also been reported. In fatal cases, death from acute hepatic failure occurs between 4 and 18 days after ingestion.

Steatosis

A patient presenting with steatosis generally shows fatigue, nausea, vomiting, hypoglycaemia and confusion. Jaundice is present in severe cases.

Acute hepatitis

Acute hepatitis may present with a prodromal illness with non-specific symptoms or include features of drug allergy followed by anorexia, nausea and vomiting, dark urine, pale stools and jaundice. Jaundice tends to be present in severe cases. Weight loss may also be a feature of acute hepatitis. Fatalities occur in 5–30% of jaundiced patients. Acute hepatitis is second only to paracetamol self-poisoning as a cause of DILD.

Chronic active hepatitis

Drug-induced chronic active hepatitis may present with tiredness, lethargy and malaise, in a manner similar to other types of chronic liver disease. The symptoms may evolve over many months. Gastro-intestinal symptoms are usually present, and patients may show one or more complications of severe liver disease, including ascites, bleeding oesophageal varices or hepatic encephalopathy. If the ADR has an allergic component, a skin rash and other extrahepatic features of a drug allergy such as lymphadenopathy, evidence of bone marrow suppression (particularly petechial haemorrhages) may be present.

Cholestasis

The main clinical feature of pure cholestasis is severe pruritus, with or without other features, according to the severity, such as dark urine, pale stools and jaundice.

Drug-induced cholestatic hepatitis usually presents with gastro-intestinal symptoms following an influenza-like illness. Abdominal pain with typical features of cholestasis then occurs. The pruritus is generally less severe than with pure cholestasis.

Veno-occlusive disease

Veno-occlusive disease may present with painful hepatomegaly, ascites and jaundice along with other features of liver insufficiency. It has been reported following chemotherapy with drugs such as cyclophosphamide, doxorubicin and dacarbazine. It has also been reported as a common complication of bone marrow transplantation.

Hepatic tumours

In general, patients with hepatic tumours present in a similar manner. Abdominal pain may or may not be reported, together with a feeling of fullness after eating. Weight loss, fatigue, anorexia, nausea and, occasionally, vomiting can occur, especially in advanced cases.

Investigations

Various types of investigation are used in the diagnosis of drug-induced hepatotoxicity, with the number and type of tests depending on the clinical presentation. Unfortunately, available laboratory tests do not provide ideal markers for DILD and the diagnosis is generally one of exclusion.

Biochemical tests

Routine LFTs are measured, which generally include total bilirubin, alanine transaminase and alkaline phosphatase. Impairment of the synthetic function of the liver is detected by total protein, albumin and the prothrombin time. Other biochemical tests may include measurement of γ-glutamyl transpeptidase which may be elevated in all forms of liver disease, including drug-induced disease. α-Fetoprotein may be measured to exclude malignancy. Conjugated bilirubin may be measured to establish if there is biliary obstruction.

Serological markers

Serological markers for hepatitis A, B and C and other viruses such as the Epstein–Barr virus should be determined in patients with symptoms of hepatitis with appropriate risk factors to exclude an infective cause.

Radiological investigations

Radiological investigations, such as ultrasound, computed tomography, percutaneous cholangiograms and endoscopic retrograde cholangiopancreatography (ERCP), are used to look for physical obstruction of bile ducts by gallstones, masses or strictures.

Liver biopsy

Liver biopsy is seldom helpful for diagnosis but certain drugs can cause characteristic lesions, such as the distribution of microvesicular fat droplets seen with tetracyclines. Specific diagnostic tests for drug-induced disease exist for few drugs, with halothane being a notable exception.

Other causes of liver dysfunction such as autoimmune chronic active hepatitis, acute severe cholestasis, ischaemic hepatic necrosis, pregnancy-related liver disease, the Budd–Chiari syndrome, rare metabolic disorders or liver disease related to alcohol abuse must also be excluded.

Treatment

The aim of treatment for drug-induced hepatotoxicity is complete recovery. This relies on correct diagnosis, withdrawal of any and all suspected drugs, and supportive therapy, which may include liver transplantation where appropriate.

Diagnosis

Drug-induced hepatic injury should be suspected in every patient with jaundice while ruling out other causes of liver disease by the clinical history and the results of investigations. The typical process in screening patients presenting with jaundice is outlined in Fig. 15.2 and the general approach to the differential diagnosis of acute hepatitis is set out in Fig. 15.3.

Drugs that are commonly prescribed, such as NSAIDs, antimicrobials and antihypertensive agents, are more likely to be implicated in DILD, although the frequency for the individual agents is low. Identifying the causative agent and stopping it is important in reducing the morbidity and mortality associated with DILD. Recovery normally follows discontinuation of a hepatotoxic drug. Serious toxicity or ALF may result if the drug is continued after symptoms appear or the serum transaminases rise significantly. Failure to discontinue the drug may give grounds for claims of negligence.

A detailed and thorough drug history, including use of oral contraceptives, over-the-counter medicines, vitamins, herbal preparations and illicit drug use, should be obtained. Examples of herbal and dietary preparations implicated in causing liver damage are listed in Box 15.1. Attention to the duration of treatment with a specific drug and the relationship to the onset of symptoms is important. The likelihood of a drug-related disease is greatest when the abnormality begins between 5 and 90 days after taking the first dose and within 15 days of taking the last dose. The latent period, that is, the time between starting therapy and the appearance of

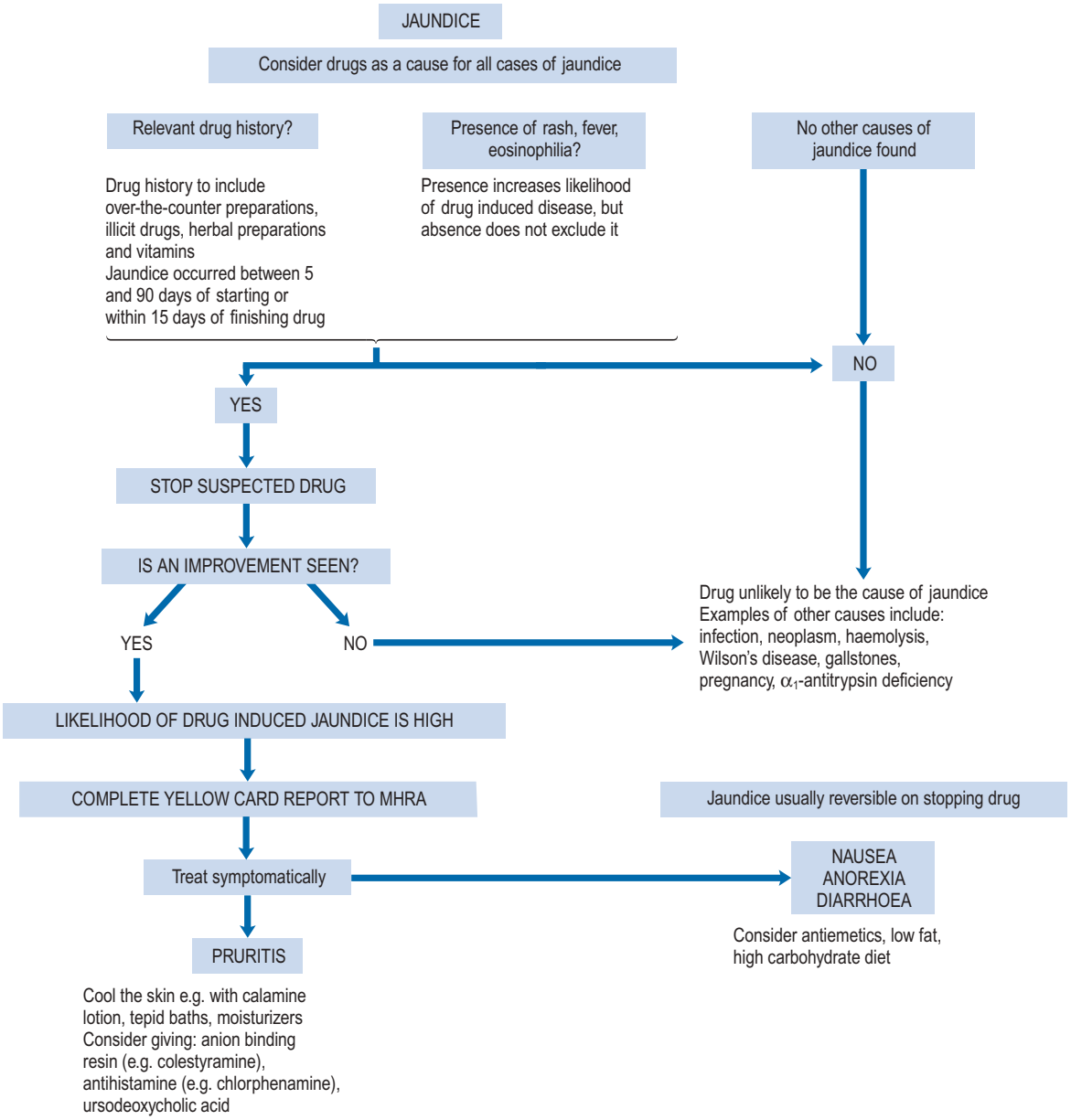


Fig. 15.2 General approach to the diagnosis and management of drug-induced jaundice.

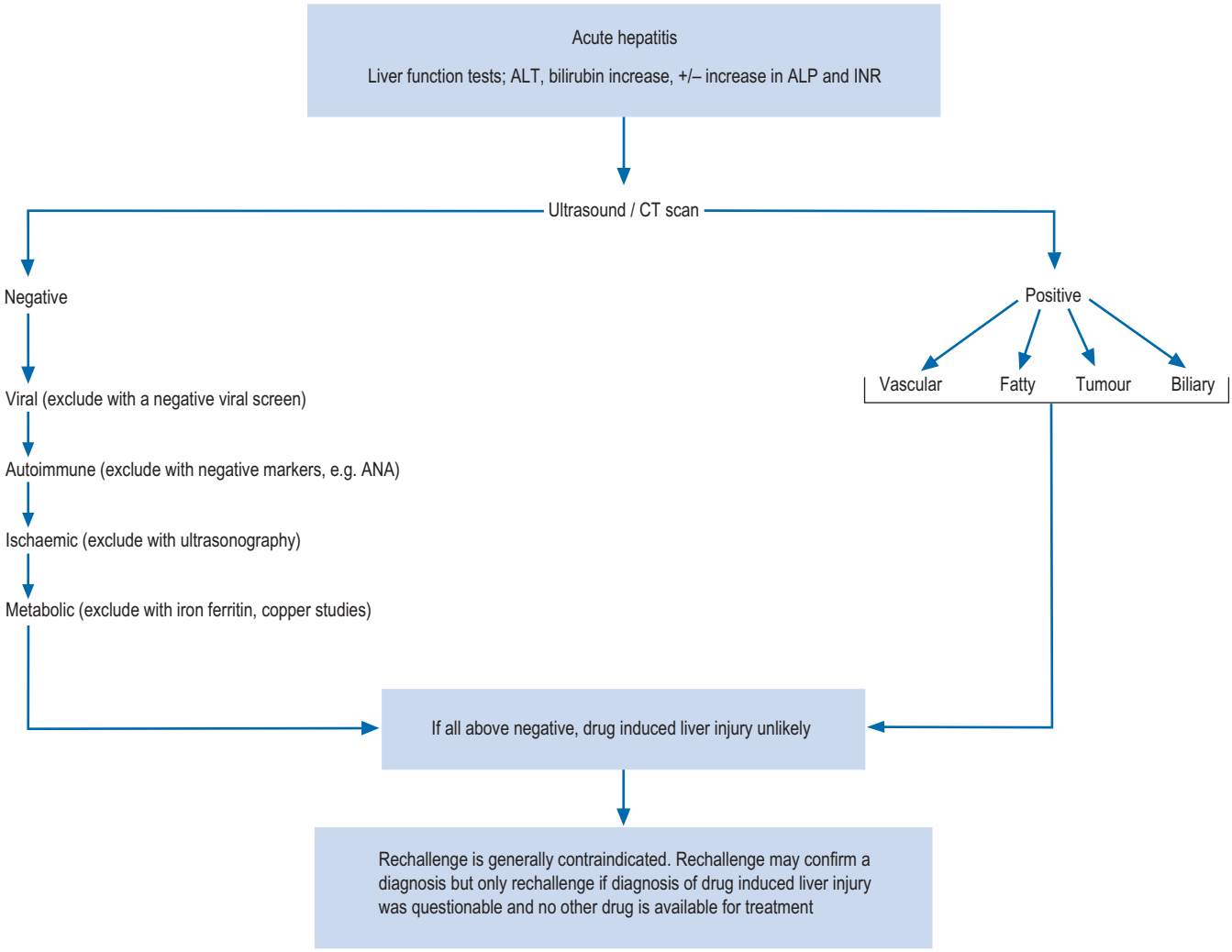
symptoms, may vary but for many drugs is sufficiently reproducible to be of some diagnostic value.

Predisposing factors for liver toxicity should also be noted. If the liver injury is accompanied by fever, rash and eosinophilia, the likelihood of drug-induced disease increases, although lack of these features does not exclude it. Unequivocal diagnosis cannot be made in most circumstances, and improvement on withdrawal of the implicated drug may provide the strongest evidence for drug-induced disease. Time for resolution of the abnormalities is dependent on the individual drug and type of liver disease. In some cases, several months may elapse.

Idiosyncratic reactions may also need to be considered and the literature consulted for previous reports. A key component of secondary prevention is the reporting of all suspected hepatic drug reactions to the appropriate monitoring agency, particularly for newer agents with fewer published cases. Many drugs are approved and licensed before the idiosyncratic reactions are identified as there is little chance of detecting the reaction in the phase III studies which typically involve 300 patients. To detect a single case of clinically significant hepatic injury due to a drug with 95% confidence, the number of patients included in the trial must be about three times the incidence of the reaction. Idiosyncratic reactions occur in about 1 in 10,000 patients so to detect the reaction, the clinical trial would have to study 30,000 patients. Practice points for diagnosing DILD are shown in Box 15.2.

Withdrawal

Once drug-induced hepatotoxicity has been recognised as a possibility, therapy should be stopped. If the patient is receiving more than one potentially hepatotoxic drug, all drugs



ALT = alanine transaminase, ALP = alakaline phosphatase, INR = international normalised ratio, ANA = antinuclear bodies

Fig. 15.3 General approach to the differential diagnosis of acute hepatitis. ALT, alanine transferase; ALP, alkaline phosphatase; INR, international normalised ratio; ANA, antinuclear antibodies.

Box 15.1 Examples of herbal remedies and food supplements implicated in hepatotoxicity

Black cohosh
Borage oil
Camellia sinensis
Chapparal (*Larrea tridentata*)
Chinese herbal preparations for skin disorders
Comfrey
Fortorol (food supplement which may contain nimesulide)
Garcinia (*Garcinia camboge*)
Germander (*Teucrium chamaedrys*)
Hydroxycut
Kava kava (*Piper methysticum*)
Khat (*Catha edulis*)
Miradin (food supplement which may contain nimesulide)
Mistletoe (skullcap)
Noni juice (*Morina citrofolia*)
Passion flower (*Passiflora incarnata*)
Ubiquinone
Valerian (*Valeriana officinalis*)

Box 15.2 Practice points for the diagnosis of drug-induced liver disease

- Consider drugs as a cause for all cases of liver damage in patients presenting with liver disease.
- Take a careful drug history include prescription, over the counter, herbal and alternative medicines
- Has the drug implicated been previously reported to cause drug-induced liver disease?
- Does the patient have risk factors for drug-induced liver disease?
- Consider the temporal relation (onset of symptoms between 5 and 90 days after initial exposure?)
- Is there improvement on discontinuation of the suspected agent?
- Rechallenge with the suspected drug is not recommended; however, a positive rechallenge is the most definite evidence of drug-induced disease.

Box 15.3 Examples of drugs associated with the development of chronic liver disease

Amiodarone
Chlorpromazine
Diclofenac
Isoniazid
Methotrexate
Nitrofurantoin

should be stopped. Withdrawal of the agent usually results in recovery that begins within a few days. However, LFTs may take many months or even years to return to normal. Co-amoxiclav and phenytoin are examples of drugs that have been associated with a worsening of the patient's condition for several weeks after withdrawal, and a protracted recovery period of several months. Examples of drugs associated with chronic liver injury are shown in Box 15.3.

Rechallenge

When drug-induced hepatotoxicity has been confirmed by improvement on drug withdrawal, subsequent use in the patient is generally contraindicated. Rechallenge is not normally justified as this is potentially dangerous for the patient, although a positive rechallenge is the most definitive confirmation of drug-induced disease. Inadvertent rechallenge may occur. If the rechallenge is negative, this is usually taken to indicate that the patient may resume using the drug. Another adverse reaction on re-exposure to the drug precludes any further use.

Management

If clinical or laboratory signs of hepatic failure appear, hospitalisation is mandatory.

After withdrawal of the drug, attempts to remove it from the body are only relevant for acute hepatotoxins such as paracetamol, metals or toxic mushrooms such as *Amanita phalloides* (death cap).

If patients present a few hours post-ingestion, any unabsorbed drug may best be removed by gastric lavage, rather than by use of emetics.

Antidotes

Specific antidotes are acetylcysteine and methionine for paracetamol, and desferrioxamine for iron overdose. Desferrioxamine 5–10 g in 50–100 mL of water is administered orally as soon as possible after ingestion for acute iron poisoning. Parenteral desferrioxamine is indicated in addition to oral administration, to chelate absorbed iron where the plasma levels exceed 89.5 µmol/L, where the plasma levels exceed 62.6 µmol/L and there is evidence of free iron, and in patients with signs and symptoms of acute iron poisoning.

Corticosteroids

Immunosuppression with corticosteroids has been used in the management of drug-induced hepatotoxicity, but evidence indicates their use does not affect survival of patients with ALF. However, there have been anecdotal reports of impressive responses to corticosteroids that are persuasive, and it may be appropriate to conduct a short trial in rare types of drug-induced disease.

Supportive treatment

For most patients there is no specific treatment available. General supportive treatment is necessary in liver failure, with appropriate attention to fluid and electrolyte balance.

Nutritional support should be along conventional medical lines. Some patients find that a low-fat, high-carbohydrate diet provides relief from the anorexia, nausea and diarrhoea that may accompany cholestasis.

Pruritus

The main symptom of drug-induced cholestasis is pruritus due to high systemic concentrations of bile acids deposited in tissues. General measures include light clothing (avoid wool) and cooling the skin with tepid baths or calamine lotion, and a general moisturising agent such as aqueous cream. The management of liver-induced pruritus is discussed in more detail in Chapter 16.

Coagulation disorders

Coagulation disorders should be treated by correcting vitamin K deficiency with intravenous phytomenadione injection. This should correct the prothrombin time within 3–5 days. Oral phytomenadione is ineffective in cholestasis. Menadiol sodium phosphate, the water-soluble vitamin K analogue, may be effective in an oral dose of 10 mg daily. If bleeding occurs, infusion of fresh frozen plasma or clotting factor concentrates will be indicated. The administration of other fat-soluble vitamins may also be necessary. Liver transplantation is often considered the treatment of choice for patients with acute hepatic failure induced by drugs.

Long-term treatment

When the DILD is under control, consideration will have to be given to the treatment of the original condition for which the implicated drug was prescribed. In many cases, drug therapy will still be required and caution must, therefore, be exercised, as drugs with similar chemical structures may cause similar hepatotoxicity (Table 15.7).

Hepatotoxicity may occur with different derivatives of a drug. Erythromycin-induced cholestatic hepatitis has been more frequently reported with the estolate preparation than with other erythromycin esters (ethylsuccinate, stearate, propionate and lactobionate). It is not clear which part of the drug is responsible for hypersensitivity.

Table 15.7 Examples of cross-sensitivity within drug groups

	Problem	Action
Phenothiazines	Cross-sensitivity	Avoid
Tricyclics	Cross-sensitivity	Avoid
NSAIDs	Cross-sensitivity	Avoid
Isoniazid, pyrazinamide	Chemically-related	Avoid
Halothane	Avoid enflurane	Isoflurane appears safe

Paracetamol-induced hepatotoxicity

Paracetamol causes a dose-related toxicity resulting in centrilobular necrosis. It normally undergoes the phase II reactions of glucuronidation and sulphation. However, paracetamol is metabolised by cytochrome P450 2E1 to *N*-acetyl-*p*-benzoquinoneimine (NABQI) if the capacity of the phase II reactions is exceeded or if cytochrome P450 2E1 is induced. After normal doses of paracetamol, NABQI is detoxified by conjugation with glutathione to produce mercaptopurine and cysteine conjugates. Following overdose, tissue stores of glutathione are depleted, allowing NABQI to accumulate and cause cell damage. Illness, starvation and alcohol deplete glutathione stores and increase the predisposition to paracetamol toxicity, while acetylcysteine and methionine provide a specific antidote by replenishing glutathione stores.

Ingestion of doses as low as 10–15 g of paracetamol have been reported to cause severe hepatocellular necrosis. Removal of unabsorbed paracetamol by gastric lavage may be worthwhile if more than 150 mg/kg body weight has been taken and the patient presents within 4 h of ingestion. Activated charcoal may also be administered to reduce further absorption of paracetamol and facilitate removal of unmetabolised paracetamol from extracellular fluids. This may lessen the effect of any methionine given. A plasma paracetamol concentration should be taken as soon as possible but not within 4 h of ingestion due to the fact that a misleading and low level may be obtained because of continuing absorption and distribution of the drug. The plasma concentration measured should be compared with a standard nomogram reference line of a plot of plasma paracetamol concentration against time in hours after ingestion. This may be a semilogarithmic (Fig. 15.4) or linear (Fig. 15.5) plot. Generally, administration of intravenous acetylcysteine is the treatment of choice for paracetamol overdose when the blood paracetamol level is in the range predictive of possible or probable liver injury (see Fig. 15.4). Patients allergic to acetylcysteine may receive oral methionine.

Acetylcysteine is most effective within 8 h of overdose. However, late administration in patients who present more than 16–24 h post-ingestion may be appropriate. Acetylcysteine administered at this stage will not counteract the oxidative effects of paracetamol but it may have a cytoprotective role in hepatic failure, and has been shown to reduce morbidity and mortality in patients who have already developed ALF.

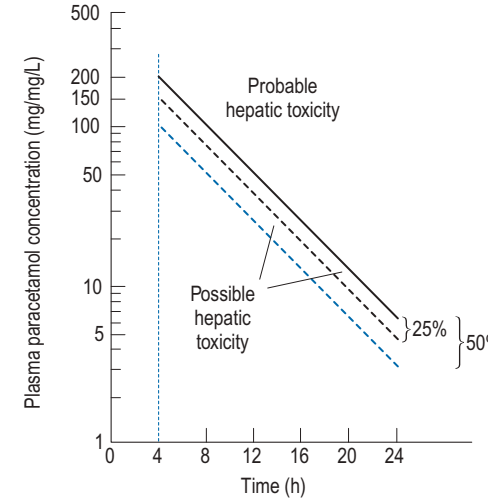


Fig. 15.4 Semilogarithmic plot of plasma paracetamol concentration versus time in hours after ingestion.

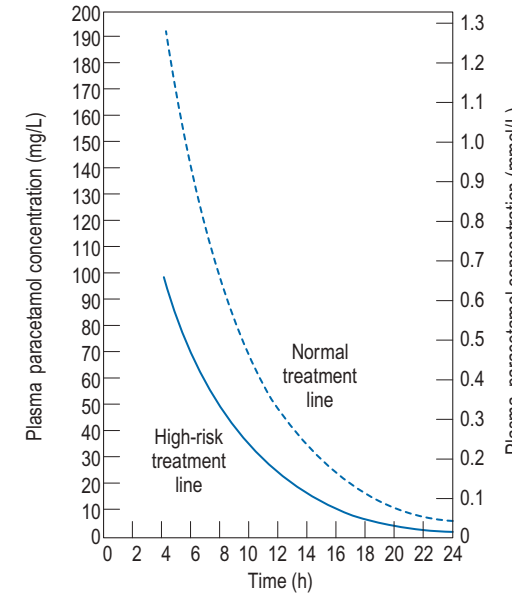


Fig. 15.5 A linear plot of plasma paracetamol concentration versus time in hours after ingestion.

Patient care

Patients may be at risk of drug-induced hepatotoxicity from prescribed drugs or from purchased drugs. Additionally, children may be at risk from medicines that are not stored properly. Parents should be reminded to store all medicines in child resistant containers and out of reach. Deaths from liver failure have occurred in children following overdose with drugs commonly available, such as iron tablets.

Patient counselling

Patients who purchase preparations containing paracetamol should be made aware of the danger of overdosing, which may occur if other preparations containing paracetamol are taken simultaneously. Since 1994 the European guidelines on package labelling have required products containing paracetamol to warn patients of the need to avoid other products containing paracetamol. The pack size of paracetamol sold from general sales outlets has been limited to 16 tablets or capsules (32 where paracetamol is sold under the supervision of a pharmacist) with the aim of limiting availability and reducing residual stocks in the home. This appears to have reduced the incidence of ALF secondary to paracetamol overdose.

All patients should be advised of potential side effects. This information needs to be reinforced with the use of patient information leaflets.

Patients and their carers should be helped to recognise signs of liver disorder and know to report immediately symptoms such as malaise, nausea, fever and abdominal discomfort that may be significant, although non-specific during the first few weeks of any change of therapy. If these are accompanied by elevated LFTs, the drug should be discontinued.

Patients who recover from drug-induced hepatotoxicity should be informed of the causative agent, warned to avoid it in the future, and advised to inform their doctor, dentist, nurse and pharmacist about the occurrence of such an event.

Parents of children commenced on sodium valproate should be warned to report side effects that may be suggestive of liver injury such as the onset of anorexia, abdominal discomfort, nausea and vomiting. Early features include drowsiness and disturbed consciousness. Fever may also be present. The time to onset is between 1 and 4 months in the majority of cases.

The challenge for all members of the health care team is to alert patients to the potentially toxic effects of drugs without creating so much concern that they fail to comply with vital medication. For the limited number of drugs presented in Table 15.8, careful monitoring of LFTs during the first 6 months of treatment is advisable, although not always practical. Thereafter, regular monitoring of LFTs is appropriate in patients who are at greater risk of hepatotoxicity. Such patients would include those with known liver disease, those taking other hepatotoxic drugs, those aged over 40 years, and heavy alcohol consumers. Surveillance should be particularly frequent in the first 2 months of treatment. In patients with no risk factors and normal pretreatment liver function, LFTs

Table 15.8 Examples of drugs where regular monitoring of liver function is recommended

Drug	Baseline measurement[a]	Frequency of monitoring
Anti-TB therapy (isoniazid, rifampicin, pyrazinamide)	Yes	Patients with pre-existing chronic liver disease: check LFTs regularly, every week for the first 2 weeks, then twice a week for the first 2 months. Patients with normal liver function tests and no evidence of pre-existing liver disease: regular monitoring is not necessary but LFTs repeated if signs of liver dysfunction develop, for example, fever, malaise, vomiting or jaundice. Patients with raised pretreatment hepatic transaminases: Two or more times normal: check LFTs weekly for 2 weeks, then twice a week until normal. Under two times normal: check LFTs at 2 weeks. If these transaminases have fallen, further tests are only needed if symptoms occur
Amiodarone	Yes	LFTs checked every 6 months
Cyproterone	Yes	Recheck if any symptoms
Dantrolene	Yes	Repeat LFTs after first 6 weeks of therapy
Itraconazole	Yes	Monitor LFTs if therapy continues for more than 1 month. Recheck if any symptoms
Ketoconazole	Yes	LFTs checked on weeks 2 and 4 of therapy and then every month
Methotrexate	Yes	LFTs checked every 2 weeks for the first 2 months, then monthly for 4 months, then every 3 months
Methyldopa	Yes	Check LFTs at intervals during the first 6–12 weeks of treatment
Micafungin	Yes	Periodic monitoring of LFTs recommended. Recheck if any symptoms
Nevirapine	Yes	Check LFTs every 2 weeks for the first 2 months, then at month 3 and then regularly
Pioglitazone	Yes	Periodic monitoring of LFTs recommended. Recheck if any symptoms

Table 15.8 Examples of drugs where regular monitoring of liver function is recommended—cont'd

Drug	Baseline measurement[a]	Frequency of monitoring
Rosiglitazone	Yes	Periodic monitoring of LFTs recommended. Recheck if any symptoms.
Sodium valproate	Yes	Check LFTs regularly during the first 6 months of therapy
Statins	Yes	LFTs checked 12 weeks after initiation or after a dose increase and periodically thereafter
Sulfasalazine	Yes	LFTs checked every 2 weeks for the first 2 months, then monthly for 4 months then every 3 months
Tipranavir	Yes	Check LFTs on weeks 2, 4 and 8 of treatment and then every 2–3 months
Vildagliptin	Yes	LFTs checked every 3 months for the first year and then periodically

[a]Baseline and subsequent liver function tests (LFTs) difficult to interpret in critically ill patients as LFTs will be affected by multiple factors

need only be repeated if fever, malaise, vomiting, jaundice or unexplained deterioration during treatment occurs.

Since many drugs cause elevation of LFTs there may be difficulty in assessing when to stop a drug, particularly when treating an individual for tuberculosis or epilepsy. An empirical guideline is that the drug should be stopped if the levels of alanine transaminase exceed three times the upper limit of the reference range. Any clinical features of liver disease or drug allergy would require immediate discontinuation of the drug. Conversely, a raised γ-glutamyl transpeptidase level and elevated alanine transaminase level in the absence of symptoms often reflect microsomal induction and would not indicate drug-induced injury.

It should be noted that monitoring of LFTs is not a complete safeguard against hepatotoxicity, as some drug reactions develop very quickly, and the liver enzymes are an unreliable indicator of fibrosis.

Minimising the risk of DILD

Cholestatic jaundice has been reported to occur in about 1 in 6000 patients treated with co-amoxiclav. The risk of acute liver injury with co-amoxiclav is approximately six times that of amoxicillin and increases with treatment courses above 14 days. Hence, the indications for co-amoxiclav have been restricted to cover infections caused by amoxicillin-resistant β-lactam-producing infections.

Patients admitted for procedures requiring a general anaesthetic should be questioned about past exposure and any previous reactions to halothane. Halothane is well known to be associated with hepatotoxicity, particularly if patients are re-exposed. Repeated exposure to halothane within a period of less than 3 months should be avoided, while some increase in risk persists regardless of the time interval since last exposure. Unexplained jaundice or delayed-onset post-operative fever in a patient who has received halothane is an absolute contraindication to future use in that individual. Patients with a family history of halothane-related liver injury should also be treated with caution.

The individuals at greatest risk of halothane hepatitis are obese, post-menopausal women. Halothane may be present in detectable amounts even in theatres equipped with scavenging devices, and it is possible for these small concentrations to provoke a reaction in a highly sensitised individual. If electing to avoid halothane, a halothane-free circuit and operating theatre should be used. Cross-hepatotoxicity with other haloalkanes is a possibility, and enflurane should also be avoided. Isoflurane appears to be safe, as no reports of cross-sensitivity have been published. Some anaesthetists would prefer to use total intravenous anaesthesia in patients who have had a reaction to halothane.

Although hepatic ADRs are rare for most drugs, when they do occur they can cause significant morbidity and mortality. Over 600 drugs have been associated with hepatotoxicity and any new drug released on to the market may have the potential to cause hepatotoxicity. Pemoline, troglitazone and tolcapone are examples of drugs withdrawn from the market due to reports of serious hepatic reactions. These examples help to highlight the importance of post-marketing surveillance and yellow card reporting.

Appropriate selection of drugs, an awareness of predisposing factors and avoidance of toxic dose thresholds and potentially hepatotoxic drug–drug interactions will minimise the risk to patients.

Practice points for patient care and minimising the risk of DILD are outlined in Box 15.4.

Box 15.4 Practice points for minimising the risk of drug-induced liver disease (DILD)

- Minimise DILD by ensuring appropriate monitoring of drugs associated with hepatotoxicity.
- Minimise DILD by following recommendations, for example, use co-amoxiclav for penicillin β-lactam resistant infections only, counsel all patients on paracetamol not to exceed 4 g/day and to be alert to other preparations containing paracetamol.
- Counsel all patients (or carers of patients) on potentially hepatotoxic medicines to recognise and report signs of liver damage.
- Inform all patients who have DILD of the causative agent, and the importance of avoiding this in future.

Case studies

Case 15.1

Mr V, a 39-year-old male, presented to his local hospital following a paracetamol overdose. He had recently separated from his wife, had not been eating properly, went on an alcohol binge and then on impulse had taken approximately 70 paracetamol tablets. He self-referred himself to his local hospital 28 h after the overdose. At presentation he was feeling nauseous and had right subcostal pain. His results at this time were:

	Actual value (normal range)
Paracetamol	18 mg/mL
Albumin	26 g/dL (30–50 g/L)
Alanine transaminase	5435 units/L (0–50 units/L)
Bilirubin	50 µmol/L (<17 µmol/L)
Alakline phosphatase	66 units/L (30–135 units/L)
Prothrombin time	57 s (9.8–12.6 s)
Creatinine	133 (35–125 µmol/L)
Urea	5.6 (0–7.5 mmol/L)

***Other test results*:**
Hepatitis screen negative
Autoantibody screen negative

At this stage, supportive treatment was given. However, he deteriorated, with worsening test results and the development of encephalopathy. He was then transferred to a tertiary intensive care unit, with a diagnosis of ALF secondary to paracetamol overdose. His test results on admission to the intensive care unit were:

	Actual value (normal range)
Albumin	22 g/dL (30–50 g/L)
Alanine transaminase	12,477 units/L (0–50 units/L)
Bilirubin	71 µmol/L (<17 µmol/L)
Alakline phosphatase	73 units/L (30–135 units/L)
Prothrombin time	90.8 s (9.8–12.6 s)
Arterial pH	7.226 (7.350–7.450)
Lactate	6.9 (0.4–2.2 mmol/L)
Creatinine	336 (35–125 µmol/L)
Urea	7.4 (0–7.5 mmol/L)

He was put on the liver transplant urgent list and received an orthotopic liver transplant (OLT) the following day.

Questions

1. What risk factors does Mr V have which suggest a worse prognosis?
2. On initial presentation what treatment should be initiated?
3. What is the significance of the high creatinine result?
4. Can Mr V be prescribed paracetamol for pain relief?

Answers

1. The progression of paracetamol toxicity can be categorised into four stages: preclinical, hepatic injury, hepatic failure, and recovery. The prognosis varies depending upon the stage at presentation. Mr V's late presentation to hospital also increases his risk of a worse prognosis. He presented to hospital 28 h after the overdose, with raised ALT and some symptoms of liver injury, indicating that he was in the hepatic injury stage and progressed onto the liver failure stage with the development of encephalopathy. Patients presenting with liver injury have a variable prognosis but patients who present with hepatic failure have a mortality rate of 20–40%. Had he presented in the preclinical stage he would have been expected to make a full recovery with treatment.

   Although Mr V had acutely ingested alcohol at the time of paracetamol overdose, this is not a risk factor for a worse prognosis. Theoretically, acute alcohol ingestion competes with paracetamol for CYP2E1 metabolism resulting in lower formation of NAPQI and thus less toxicity. Chronic alcohol consumption induces the CYP2E1 enzyme resulting in increased NAPQI production and increased risk of hepatotoxicity.

   The fact that Mr V had not been eating properly may have resulted in depleted glutathione stores and a worse prognosis.

   Mr V developed hepatorenal syndrome, this is a poor prognostic indicator and has an associated mortality of 50–100%. A poor prognosis is also associated with the following:

Prothrombin time	>36 s
Creatinine	>200 µmol/L
pH	<7.3
Encephalopathy	Present
Cerebral oedema	Present
Time from onset of jaundice to encephalopathy	0–7 days

2. A plasma paracetamol level needs to be taken as soon as possible, although not within the first 4 h following paracetamol overdose. A toxic screen should be performed to exclude other drug overdoses. Supportive therapy with intravenous fluids and oxygen, if necessary, should be given. This patient should also be treated with *N*-acetylcysteine. Treatment with *N*-acetylcysteine is particularly beneficial when administered within 8 h of paracetamol overdose when the blood paracetamol level is in the range predictive of possible or probable liver injury (see Fig. 15.4). However, late administration in patients who present more than 16–24 h post-ingestion is also appropriate. Acetylcysteine administered at this stage will not counteract the oxidative effects of paracetamol but it may have a cytoprotective role in hepatic failure, improving haemodynamics and oxygen use. Late administration of *N*-acetylcysteine has been shown to reduce morbidity and mortality in patients who have already developed hepatic failure. Available data for use of *N*-acetylcysteine following paracetamol overdose suggests that, although the evidence for benefit is limited, it should be given to patients with overdose (Brok et al., 2006).
3. Mr V developed renal impairment secondary to the liver damage which is known as the hepatorenal syndrome (HRS). Other causes of renal impairment should be excluded. Where necessary drug doses should be adjusted for renal impairment. Once the liver recovers, or transplantation of the liver occurs, the kidneys are likely to recover.
4. Paracetamol should be avoided in the acute phase following an overdose. However, if following the acute phase, the patient needs either an analgesic or antipyretic, then paracetamol in small doses may be used. Following a liver transplant, standard paracetamol doses can be used as long as the patient is adequately nourished and does not have any psychological issues with the use of paracetamol.

Case 15.2

Ms B is a 43-year-old lady with type 2 diabetes who was commenced on simvastatin 10 mg at night 4 months ago. She has no other relevant past medical history. She does not drink alcohol and does not consume grapefruit. Drug history includes gliclazide MR 60 mg twice a day and aspirin 75 mg daily. A routine blood test revealed an increase in ALT from baseline (pre-simvastatin) of 21 to 197 units/L (0–50 units/L) at 4 months.

Questions

1. What are the likely causes of the increase in ALT?
2. Should liver function tests be routinely monitored in patients on a statin?
3. What action, if any, should be taken in this case?
4. Can statins be used in patients with pre-existing liver disease?

Answers

1. The most likely cause of the increase in ALT is the introduction of simvastatin 4 months previously. All statins are reported to cause elevations in transaminases, which may be transient or persistent. The incidence of transaminitis with statins is low, being reported to occur between 1 in 1000 and 1 in 10,000 patients. Other causes of liver disease should also be considered in this case, for example, non-alcoholic steatohepatitis (NASH) associated with diabetes.
2. Monitoring of liver function tests in patients taking a statin is recommended in the Summary of Product Characteristics, and hence should be monitored for medico legal reasons (McKenney et al., 2006). It is recommended to monitor liver function tests at baseline and then at 12 weeks or after a dose increase. However, the true value for monitoring liver function test is not clear as it does not identify those at risk of liver damage, is expensive and may lead to patient anxiety and unnecessary cessation of statin therapy. Moreover, hepatic function does not appear to be compromised by statin use and there is no apparent link between an elevation in liver function tests and the development of toxicity (McKenney et al., 2006).
3. Ms B had a single high ALT result. The general recommendation is that if the patient is asymptomatic and the transaminase levels are greater than three times the upper limit of normal the test should be repeated. If transaminases are still more than three times upper limit of normal the patient should have a full liver investigation.

   In this case, the simvastatin was switched to pravastatin before a repeat liver function test. Follow-up liver function tests showed that the ALT had returned to within the normal range. It is highly probable that this rise in ALT on simvastatin would have been transient and had the patient continued with simvastatin the ALT would have normalised. However, the patient was anxious, did not want to risk any progression of liver toxicity and was keen to switch to an alternative statin.
4. Statins are contraindicated in ALF and decompensated chronic liver disease. However, they can probably be used safely in liver disease where there is no, or mild, synthetic dysfunction. Statin use may actually improve elevations in transminases in patients with fatty liver disease (Gomez-Dominguez et al., 2006)

Case 15.3

Mr K, a 28-year-old HIV-infected male, was found to have elevated liver function tests on a routine monitoring sample following initiation of antiretroviral therapy. He had previously been diagnosed with HIV 6 months ago, with a CD count of 330 cells/mm³ and a viral load of 83,000 copies/mL. Relevant past medical history included psychiatric illness. He had been initiated on Kivexa® (abacavir and lamivudine) and nevirapine 5 months ago. He is not on any other medications. Mr K was recalled to the hospital clinic for urgent medication review. In the clinic, Mr K reported a 3-day history of general malaise, abdominal discomfort and nausea. Examination in clinic showed to have a normal blood pressure, a temperature of 37.1 °C and slight visible jaundice. There were no signs of a hypersensitivity reaction. His routine liver function tests were:

	Actual value (normal range)
Albumin	**30 g/dL (30–50 g/L)**
Alanine transaminase	**350 units/L (0–50 units/L)**
Bilirubin	**90 µmol/L (<17 µmol/L)**
Alkaline phosphatase	**180 units/L (30–135 units/L)**

Questions

1. For which drug would Mr K be having routine liver function tests?
2. What is the significance of looking for signs of hypersensitivity?
3. Does Mr K have any risk factors for developing drug associated hepatotoxicity?
4. What actions should be taken in relation to this patient's antiretroviral therapy?

Answers

1. Hepatotoxicity among HIV-infected persons taking nevirapine is a well recognised adverse effect. The incidence of an asymptomatic increase in hepatic aminotransferase levels is reported as approximately 5–15%, with the incidence of clinically symptomatic hepatitis among persons taking nevirapine of approximately 4% (Martínez et al., 2001). It is recommended that all patients commencing on nevirapine undergo close monitoring during the first 18 weeks of treatment, with liver function tests performed at baseline, then every 2 weeks for the first 2 months again after a further 1 month and regularly thereafter.
2. Signs of hypersensitivity help to diagnose the type of nevirapine induced hepatotoxicty. Two distinct mechanisms and time courses of nevirapine-associated hepatotoxicity have been recognised. The first type is an immune-mediated hypersensitivity reaction, developing within 18 weeks of the start of nevirapine. Most patients with this type of early nevirapine associated hepatotoxicity will have concomitant flu-like symptoms (fever, myalgia, fatigue, malaise, nausea, and vomiting) with or without skin rash. The second, and much less frequent type, typically occurs after 18 weeks of nevirapine therapy and most likely represents an intrinsic toxic drug effect (Soriano et al., 2008).
3. Mr K does not have any risk factors. Risk factors for developing hepatotoxicity with nevirapine include female gender, higher CD4 cell count prior to starting nevirapine (greater than 250 cells/mm³ in females and greater than 400 cells/mm³ in males), chronic hepatitis B or C virus infection, alcoholic liver disease and abnormal baseline hepatic aminotransferase levels (Soriano et al., 2008).
4. In general, nevirapine should be discontinued when increases in hepatic aminotransferase levels occur associated with a rash. Mr K shows signs of clinical hepatitis with symptoms of general malaise, abdominal discomfort and nausea, in conjunction with a raised ALT. He does not show signs of hypersensitivity or rash. His nevirapine therapy should be suspended and his liver function monitored closely. Once his liver function has settled, nevirapine could be cautiously reintroduced with close monitoring. For patients who develop nevirapine-associated hepatitis, the risk of developing hepatitis from subsequent treatment with efavirenz or delavirdine remains unknown. As a consequence, efavirenz or delavirdine should be used with caution if initiated in a patient with prior nevirapine-associated hepatotoxicity.

Acknowledgement

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16 Liver disease

P. Kennedy and J. G. O'Grady

Key points

- The liver is a complex organ central to the maintenance of homeostasis.
- The liver is notable for its capacity to regenerate unless cirrhosis has developed. There are now some data to suggest that cirrhosis is reversible in selected cases, for example treated hepatitis B virus.
- The spectrum of liver disease extends from mild, self-limiting conditions to serious illnesses which may carry significant morbidity and mortality.
- Liver disease is defined as acute or chronic on the basis of whether the history of disease is less than or greater than 6 months, respectively.
- Viral infections and paracetamol overdose are the leading causes of acute liver disease, but a significant number of patients have no defined aetiology (seronegative hepatitis).
- Alcohol abuse and chronic viral hepatitis (B and C) are the major causes of chronic liver disease.
- Cirrhosis may be asymptomatic for considerable periods of time.
- Ascites, encephalopathy, varices and hepatorenal failure are the main serious complications of cirrhosis.
- A careful assessment is required prior to the use of any drug in a patient with liver disease due to unpredictable effects on drug handling.

The liver weighs up to 1500 g in adults and as such is one of the largest organs in the body. The main functions of the liver include protein synthesis, storage and metabolism of fats and carbohydrates, detoxification of drugs and other toxins, excretion of bilirubin and metabolism of hormones, as summarised in Fig. 16.1. The liver has considerable reserve capacity reflected in its ability to function normally despite surgical removal of 70–80% of the organ or the presence of significant disease. It is noted for its capacity to regenerate rapidly. However, once it has been critically damaged multiple complications develop involving many body systems. The distinction between acute and chronic liver disease is conventionally based on whether the history is less or greater than 6 months, respectively.

The hepatocyte is the functioning unit of the liver. Heptocytes are arranged in lobules and within a lobule hepatocytes perform different functions depending on how close they are to the portal tract. The portal tract is the 'service network' of the liver and contains an artery and a portal vein delivering blood to the liver and bile duct which forms part of the biliary drainage system (Fig. 16.2). The blood supply to the liver is 30% arterial and the remainder is from the portal system which drains most of the abdominal viscera. Blood passes from the portal tract through sinusoids that facilitate exposure to the hepatocytes before the blood is drained away by the hepatic venules and veins. There are a number of other cell populations in the liver, but two of the most important are Kuppfer cells, fixed monocytes that phagocytose bacteria and particulate matter, and stellate cells responsible for the fibrotic reaction that ultimately leads to cirrhosis.

Acute liver disease

Acute liver disease is a self-limiting episode of hepatocyte damage which in most cases resolves spontaneously without clinical sequelae. This is a rare condition in which there is a rapid deterioration in liver function with associated encephalopathy (altered mentation) and coagulopathy. Acute liver failure (ALF) carries a significant morbidity and mortality and may require emergency liver transplantation.

Chronic liver disease

Chronic liver disease occurs when permanent structural changes within the liver develop secondary to long-standing cell damage, with the consequent loss of normal liver architecture. In many cases, this progresses to cirrhosis, where fibrous scars divide the liver cells into areas of regenerative tissue called nodules (Fig. 16.3). Conventional wisdom is that this

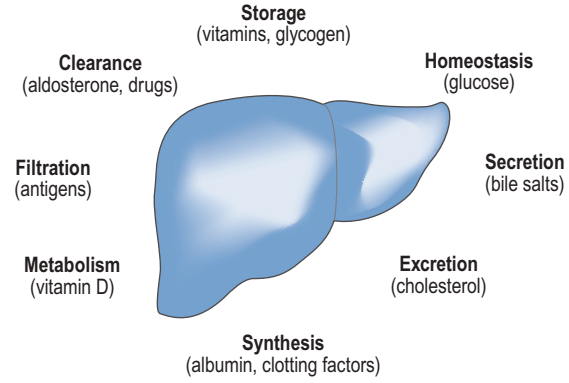

Fig. 16.1 Normal physiological functions of the liver, with examples of each.

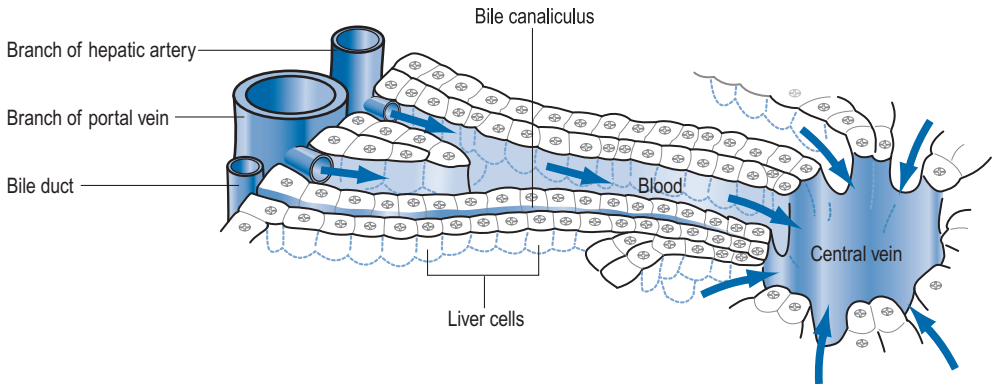

Fig. 16.2 Illustration of the relationship between the three structures that comprise the portal tract, with blood from both the hepatic artery and portal vein perfusing the hepatocytes before draining away towards the hepatic veins (central veins). Each hepatocyte is also able to secrete bile via the network of bile ducts. (Reproduced with permission of McGraw-Hill from Vander, 1980.)

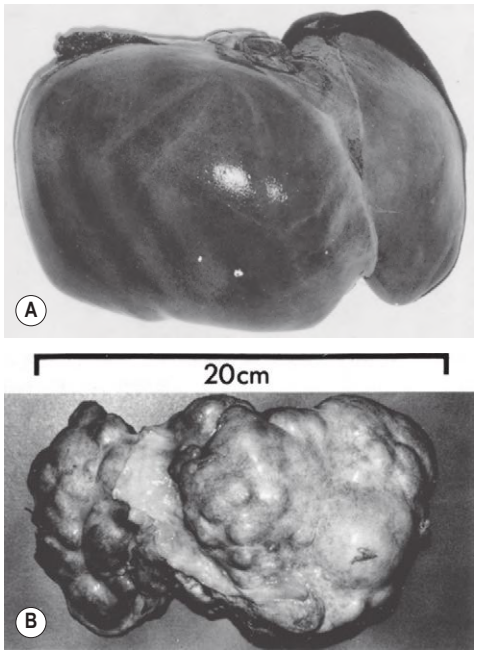

Fig. 16.3 The gross post-mortem appearance of (A) a normal and (B) a cirrhotic liver demonstrating scarring and nodule formation in part B.

process is irreversible, but therapeutic intervention in hepatitis B and haemochromatosis has now repeatedly documented cases of reversal of cirrhosis. Once chronic liver disease progresses, patients are at risk of developing liver failure, portal hypertension or hepatocellular carcinoma. Cirrhosis is a sequel of chronic liver disease of any aetiology and it develops over very variable time periods from 5 to 20 or more years.

Causes of liver disease

Viral infections

Viruses commonly affect the liver, resulting in a transient and innocuous hepatitis. Viruses which target the liver are primarily described as hepatotropic viruses, and each of these can lead to clinically significant hepatitis and in some cases to the development of chronic viral hepatitis with viral persistence. Five human viruses have been well described to date, including hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and E (HEV). Each type of viral hepatitis causes a similar pathology with acute inflammation of the liver. Types A and E are classically associated with an acute and sometimes severe hepatitis which is invariably self-limited, but occasionally fatal. Hepatitis B causes acute hepatitis in adults and 5% of patients become chronic carriers, while 95% of patients infected in the neonatal period are chronically infected. Hepatitis C rarely causes an acute hepatitis but up to 85% of patients become chronic carriers. Both viruses cause chronic liver inflammation or hepatitis, cirrhosis and hepatocellular carcinoma.

Hepatitis A

Hepatitis A virus (HAV) is a non-enveloped RNA virus and a major cause of acute hepatitis worldwide, accounting for up to 25% of clinical hepatitis in the developed world. HAV is an enteric virus and the faecal oral route is the main mechanism of transmission. The virus is particularly contagious and constitutes a public health problem throughout the world. The virus may go unnoticed by the patient in the absence of an icteric episode, particularly in children. However, HAV can cause ALF in less than 1% of patients who are typically older adults. The virus is particularly prevalent in areas of poor sanitation, and often associated with water- and food-borne epidemics. Hepatitis A has a relatively short incubation period (2–7 weeks), during which time the virus replicates and abnormalities in liver function tests can be detected.

Hepatitis B

Up to 500 million people worldwide are chronically infected with the hepatitis B virus (HBV). Chronic HBV is defined as the presence of hepatitis B surface antigens (HBsAg) for a period of more than 6 months. In endemic areas of Africa and the Far East, up to 15–20% of the population are chronic carriers of HBV and exposure to HBV at birth (vertical transmission)

is the single most important risk factor for the development of chronic HBV infection. Acquisition of HBV in adulthood is often via sexual transmission and is usually associated with a discrete episode of hepatitis. HBV can also be transmitted parenterally, by the transfusion of blood or blood products from contaminated stocks and by intravenous drug use or needle sharing.

There are many factors that determine the outcome of HBV infection, ranging from age and genetic factors of the host to virus characteristics. Acute HBV infection has a peculiarly long incubation period of 3–6 months, which is generally self-limiting and does not require antiviral therapy. Most patients recover within 1–2 months of the onset of jaundice. The protracted incubation period and the ability of the virus to escape the host immune response contribute to the development of chronic HBV. Chronic HBV is associated with varying levels of viraemia and hepatic inflammation. The level of viraemia, and thus infectivity, was conventionally determined by the presence of the hepatitis Be antigen (HBeAg); and HBeAg loss resulted in a reduction in HBV viraemia and a more favourable outcome. However, HBeAg negative chronic hepatitis with significantly elevated levels of HBV DNA is now recognised as a growing health care problem and is associated with a poorer prognosis. HBeAg negative chronic HBV results as a consequence of the emergence of escape mutants from the core promoter or pre-core regions of the virus. It is estimated that 15–40% of HBV carriers will develop serious sequelae during their lifetime, namely liver cirrhosis and/or hepatocellular carcinoma, which can develop in chronic HBV in the absence of cirrhosis. Childhood infection is associated with a different disease outcome with a higher percentage of patients developing chronic HBV infection, and owing to the protracted exposure to the virus a higher proportion develop cirrhosis and hepatocellular carcinoma.

Hepatitis C

Over 170 million people worldwide are chronically infected with hepatitis C virus (HCV). HCV is a hepatotropic, non-cytopathic, predominantly blood borne virus with greater infectivity than the human immunodeficiency virus (HIV). It is estimated that more than 2.7 million people in the USA are chronically infected with HCV, where it is the leading cause of death from liver disease. The equivalent estimate for the UK is between 200,000 and 500,000, although a considerable proportion of these have not yet been diagnosed. HCV is transmitted parenterally, most commonly through intravenous drug use and the sharing of contaminated needles. Prior to its identification in 1990, HCV (previously known as Non-A, Non-B viral hepatitis) was also contracted through contaminated blood and blood products. The introduction of widespread screening of blood donors and pooled blood products has largely consigned blood transfusion as a mode of transmission to history. There remains a small risk of HCV infection associated with tattooing, electrolysis, ear piercing, acupuncture and sexual contact. The vertical transmission rate from HCV infected mother to child is less than 3%.

Hepatitis D

Hepatitis D virus (HDV) is an incomplete virus that can establish infection only in patients simultaneously infected by HBV. It is estimated that 5% of HBV carriers worldwide are infected with HDV. It is endemic in the Mediterranean basin and is transmitted permucosally, percutaneously or sexually. In other geographical areas, it is confined to intravenous drug users.

HCV infection is associated with the development of a recognised episode of acute hepatitis in only a small percentage of individuals. The majority of patients remain asymptomatic and so are often unaware of the infection or the timing of when they contracted the virus. Symptoms associated with HCV infection tend to be mild constitutional upset with malaise, weakness and anorexia being most commonly reported. Up to 85% of subjects exposed to HCV develop chronic disease, which can lead to progressive liver damage, cirrhosis and hepatocellular carcinoma. Unlike HBV, the risk of developing hepatocellular carcinoma is almost totally linked to the presence of cirrhosis. Approximately 20–30% of patients with chronic HCV infection progress to end-stage liver disease within 20–30 years and alcohol consumption is a recognised co-factor that accelerates disease progression. HCV infection is now the leading worldwide indication for liver transplantation.

Hepatitis E

Hepatitis E virus (HEV) is endemic in India, Asia, the Middle East and parts of Latin America. It is an RNA virus which is transmitted enterically and leads to acute hepatitis. The symptoms of HEV are no different from other causes of viral hepatitis, with an average incubation period of 42 days. It was previously thought that the risk of death was increased in pregnancy, especially in the final trimester, but more recent data do not support this belief.

Alcohol

Alcohol is the single most significant cause of liver disease throughout the Western world accounting for between 40% and 60% of cases of cirrhosis in different countries. In general, deaths from alcoholic liver disease in each country correlate with the consumption of alcohol per head of population, although additional factors can influence this trend. Liver disease related to recent alcohol consumption presents a broad spectrum, ranging from the relatively benign fatty liver disease to the development of alcoholic hepatitis, a condition with an immediate mortality of between 30% and 60%. An estimated 20% of alcohol abusers develop progressive liver fibrosis, which can eventually lead to alcoholic cirrhosis, typically after a period of 10–20 years of heavy indulgence.

The central event in the development of hepatic fibrosis is the transformation of hepatic stellate cells into matrix secreting cells producing pericellular fibrosis. This network of collagen fibres develops around the liver cells and gradually leads to hepatocyte cell death. The extent of fibrosis progresses and micronodular fibrotic bands develop characterising alcoholic cirrhosis. The anatomical changes within the liver increase

resistance to blood flow from the portal system, causing an increase in pressure within this system resulting in portal hypertension. As the number of normally functioning liver cells reduces further, because of continued liver cell failure and death, the clinical condition deteriorates progressively with the development of liver failure. The rate of disease progression, and indeed regression, is very strongly linked to whether or not patients continue to consume alcohol.

Non-alcohol related fatty liver disease

Liver pathology that is very similar to alcohol-induced disease is now well recognised in a number of settings including obesity, diabetes mellitus and the metabolic syndrome. As a result, the entities of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have been introduced. It has been suggested that up to 25% of the U.S. population have NAFLD. The majority of cases of cryptogenic cirrhosis probably reflect the end stage of the NAFLD/NASH disease process even though by that stage the characteristic fatty infiltrate has disappeared.

Immune disorders

Autoimmune disease can affect the hepatocyte or bile duct and is characterised by the presence of auto-antibodies and raised immunoglobulin levels.

Autoimmune hepatitis (AIH)

AIH is an unresolving inflammation of the liver characterised by the presence of auto-antibodies (anti-smooth muscle [type 1] or anti-kidney, liver microsomal [type 2]), hypergammaglobulinemia and an interface hepatitis on liver histology. It is usually a chronic, progressive disease which can occasionally present acutely with a severe hepatitis. AIH typically occurs in young women, between 20 and 40 years, and often with a history or family history of autoimmune disorders.

Primary biliary cirrhosis (PBC)

PBC is an autoimmune disease of the liver which predominantly affects middle aged women (95% of cases are female). It is characterised by the presence of antimitochondrial antibodies and a granulomatous destruction of the interlobular bile ducts leading to progressive ductopenia, fibrosis and cirrhosis. The disease is progressive, albeit over a period of 20 years or longer if diagnosed at an early stage, and liver transplantation is the only effective treatment.

Primary sclerosing cholangitis (PSC)

PSC is an idiopathic chronic inflammatory disease resulting in intra- and extra-hepatic biliary strictures, cholestasis and eventually cirrhosis. There is a strong association with inflammatory bowel disease, particularly ulcerative colitis; 75% of PSC patients have ulcerative colitis and 5–8% of patients with ulcerative colitis develop PSC. It has a predeliction for young Caucasian males (mean age at presentation 39 years), but it can occur in infancy or childhood and can affect any race. Cholangiocarcinoma develops in up to 10% of patients with PSC.

Vascular abnormalities

The Budd–Chiari syndrome (BCS) is a rare, heterogeneous and potentially fatal condition related to the obstruction of the hepatic venous outflow tract. The prevalence of underlying thrombophilia is markedly increased in patients with BCS. Affected patients are commonly women with an average age at presentation of 35. Early recognition and immediate use of anticoagulation has vastly improved outcome. More advanced disease can be treated in a number of ways including venoplasty, transjugular intrahepatic portosystemic shunt (TIPS), surgical shunts or liver transplantation.

Metabolic and genetic disorders

There are various inherited metabolic disorders that can affect the functioning of the liver.

Haemochromatosis

Hereditary haemachromatosis (HH) is the most commonly identified genetic disorder in the Caucasian population. It is associated with increased absorption of dietary iron resulting in deposition within the liver, heart, pancreas, joints, pituitary gland and other organs. This can lead to cirrhosis and hepatocellular carcinoma.

Wilson's disease

Wilson's disease is an autosomal recessive disorder of copper metabolism. The disorder leads to excessive absorption and deposition of dietary copper within the liver, brain, kidneys and other tissues. Presentation can vary widely from chronic hepatitis, asymptomatic cirrhosis, ALF to neuropsychiatric symptoms with cognitive impairment.

α_1-Antitrypsin deficiency

This is an autosomal recessively inherited disease and is the most common genetic metabolic liver disease. The disease results in a reduction in α_1-antitrypsin which is protective against a variety of proteases including trypsin, chymotrypsin, elastase and proteases present in neutrophils. The homozygous form of the disease (ZZ phenotype) is associated with the development of liver disease and cirrhosis in 15–30% of both adult and paediatric patients.

Glycogen storage disease

Glycogen storage disease is a rare disease occurring in 1 in 100,000 births. Enzymatic deficiencies at specific steps in the pathway of glycogen metabolism cause impaired glucose production and accumulation of abnormal glycogen in the liver.

Gilbert's syndrome

Gilbert's syndrome is characterised by persistent mild unconjugated hyperbilirubinaemia. It is most frequently recognised in adolescents and young adults with an incidence of between 2% and 7% in the general population. Serum bilirubin levels fluctuate but can increase to 80–100 µmol/L during periods of stress, sleep deprivation, prolonged fasting, menstruation and intercurrent infections. Gilbert's syndrome is an asymptomatic condition requiring no therapy, although patients may inappropriately associate being jaundiced with the symptoms of the condition that triggered the increase in the bilirubin levels.

Drugs

Drugs are an important cause of abnormal liver function tests and acute liver injury, including ALF (DILI drug-induced liver injury). Drugs can also be relevant to a number of chronic liver diseases including steatosis, fibrosis/cirrhosis, autoimmune and vascular disease. In most situations, the drug is implicated because of an appropriate temporal relationship between the disease and drug exposure.

Clinical manifestations

Symptoms of liver disease

In patients who have liver disease, weakness, increased fatigue and general malaise are common but non-specific symptoms. Weight loss and anorexia are more commonly seen in chronic liver disease and loss of muscle bulk is a characteristic of very advanced disease. Abdominal discomfort may be described by patients with an enlarged liver or spleen while distension with ascites is usually the cause in more advanced disease. Abdominal pain is common in hepatobiliary disease, frequently localised to the right upper quadrant. This is often a feature of rapid or gross enlargement of the liver when the pain is thought to be a consequence of capsular stretching. Tenderness over the liver is a symptom of acute hepatitis, hepatic abscess or hepatic malignancy.

Jaundice is the most striking symptom of liver disease and can present with or without pain, depending on the underlying aetiology of disease. Pruritus can be a distressing symptom in cholestatic liver disease and patients usually complain that it is worse at night. Patients with acute and chronic liver disease can develop bleeding complications because of defective hepatic synthesis of coagulation factors and low platelet counts

Signs of liver disease

Cutaneous signs

Hyperpigmentation is common in chronic liver disease and results from increased deposition of melanin. It is particularly associated with PBC and haemachromatosis. Scratch marks on the skin suggest pruritus which is a common feature of cholestatic liver disease. Vascular 'spiders' referred to as spider naevi are small vascular malformations in the skin and are found in the drainage area of the superior vena cava, commonly seen on the face, neck, hands and arms. Examination of the limbs can reveal several signs, none of which are specific to liver disease. Palmar erythema, a mottled reddening of the palms of the hands, can be associated with both acute and chronic liver disease. Dupuytren's contracture, thickening and shortening of the palmar fascia of the hands causing flexion deformities of the fingers, was traditionally associated with alcoholic cirrhosis. It is now considered to be multifactorial in origin and not to reflect primary liver disease. Nail changes, highly polished nails or white nails (leukonychia) can be seen in up to 80% of patients with chronic liver disease. Leukonychia is a consequence of low serum albumin. Finger clubbing is most commonly seen in hypoxaemia related to hepato-pulmonary syndrome, but is also a feature of chronic liver disease (Table 16.1)

Abdominal signs

Abdominal distension, notably of the flanks, is suggestive of ascites which can develop in both acute (less commonly) and chronic liver disease. An enlarged liver (hepatomegaly) is a common finding in acute liver disease. In cirrhotic patients the liver may be large, but alternatively it may be small and shrunken reflecting end-stage chronic disease. An enlarged spleen (splenomegaly) in the presence of chronic liver disease is the most important sign of portal hypertension. Dilated abdominal wall veins are a notable finding in chronic liver disease with the detection of umbilical and para-umbilical veins, a feature of portal hypertension.

Jaundice

Jaundice is the physical sign regarded as synonymous with liver disease and is most easily detected in the sclerae. It reflects impaired liver cell function (hepatocellular pathology)

Table 16.1 Physical signs of chronic liver disease

Common findings	End-stage findings
Jaundice	Ascites
Gynaecomastia & loss of body hair	Dilated abdominal blood vessels
Hand changes:	Fetor hepaticus
Palmar erythema	Hepatic flap
Clubbing	Neurological changes:
Dupuytren's contracture	Hepatic encephalopathy
Leuconychia	Disorientation
Liver mass reduced or increased	Changes in consciousness
Parotid enlargement	Peripheral oedema
Scratch marks on skin	Pigmented skin
Purpura	Muscle wasting
Spider naevi	
Splenomegaly	
Testicular atrophy	
Xanthelasma	
Hair loss	

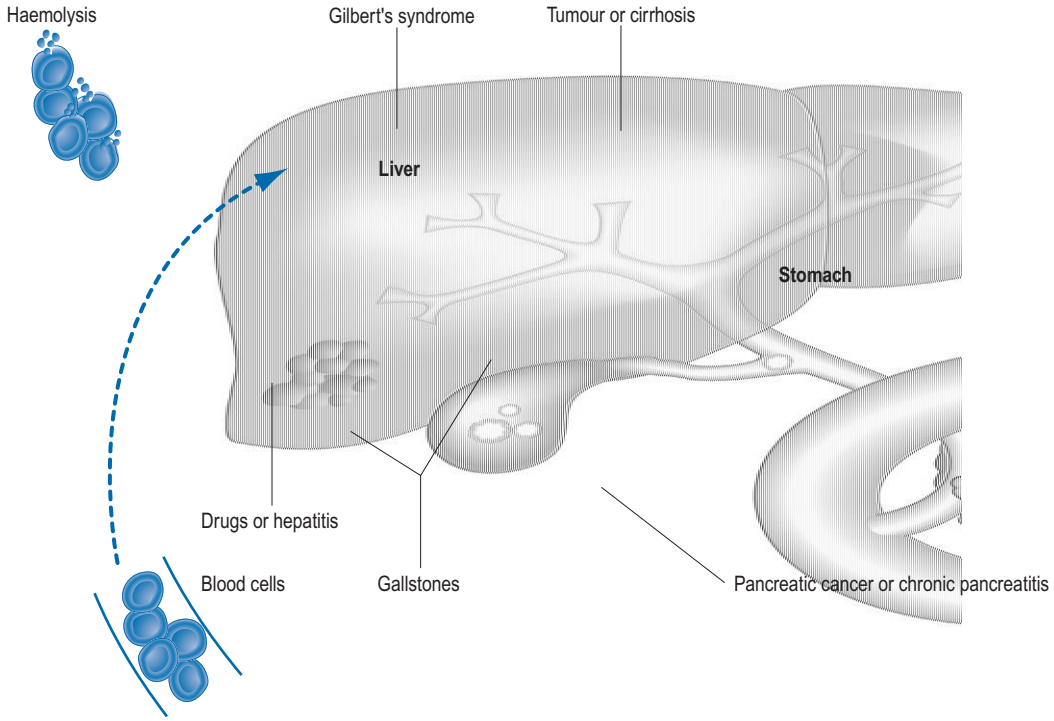

Fig. 16.4 Common causes of jaundice. Obstructive: due to blockage of the bile ducts; Hepatocellular: due to drugs, hepatitis, chronic liver disease or tumour formation; Prehepatic: due to increased blood breakdown such as occurs in haemolysis.

or it can be cholestatic (biliary) in origin. Hepatocellular jaundice is commonly seen in acute liver disease, but may be absent in chronic disease until the terminal stages of cirrhosis are reached. The causes of jaundice are shown in Fig. 16.4.

Portal hypertension

The increased pressure in the portal venous system leads to collateral vein formation and shunting of blood to the systemic circulation. Portal hypertension is an important contributory factor to the formation of ascites and the development of encephalopathy due to bypassing of blood from the liver to the systemic circulation. The major, potentially life-threatening complication of portal hypertension is torrential venous haemorrhage (variceal bleed) from the thin walled veins in the oesophagus and upper stomach. Patients with portal hypertension are often asymptomatic, while others may present with bleeding varices, ascites and/or encephalopathy.

Ascites

Ascites is the accumulation of fluid within the abdominal cavity. The precise mechanism by which ascites develops in chronic liver disease is unclear, but the following are all thought to contribute:

- Activation of the renin–angiotensin–aldosterone axis as a consequence of central hypovolaemia, leading to a reduction in sodium excretion by the kidney and fluid retention. Reduced aldosterone metabolism due to reduced liver function may also contribute to increased fluid retention.
- A reduction in serum albumin and reduced oncotic pressure is thought to contribute to the collection of fluid in the third space. Peripheral oedema (swollen lower limbs) occurs through this mechanism in a manner similar to the development of ascites.
- Portal hypertension and splanchnic arterial vasodilation alters intestinal capillary pressure and permeability and so facilitates the accumulation of retained fluid in the abdominal cavity.

Sexual characteristics

Endocrine changes are well documented in chronic liver disease and tend to be more common in alcoholic liver disease. Hypogonadism is common in patients with cirrhosis and in males results in testicular atrophy, female body hair distribution and gynaecomastia. This is thought, in part, to occur because the cirrhotic liver cannot metabolise oestrogen, leading to feminisation in males. Gynaecomastia is particularly found in alcoholics but is also seen in those taking spironolactone, when there is usually associated tenderness of the nipples. In women with chronic liver disease menstrual irregularity, amenorrhoea and reduced fertility are encountered in those of reproductive age, but few detectable physical signs are seen as a result of gonadal atrophy.

Investigations

All patients with liver disease must undergo a comprehensive and thorough assessment to ascertain the underlying aetiology. Although causes of acute and chronic liver disease may differ, a similar approach is used to investigate both patient groups to ensure no primary cause or co-factor is overlooked.

Biochemical tests

Biochemical liver function tests (LFTs) are simple, inexpensive and easy to perform but usually cannot be used in isolation to make a diagnosis. Biochemical parameters provide very useful information in monitoring disease progression or response to therapy. The liver enzymes usually measured are the aminotransferases which reflect hepatocellular pathology and the cholestatic liver enzymes, alkaline phosphatase and γ-glutamyl transpeptidase. Aspartate transaminase (AST) and alanine transaminase (ALT) are two intracellular enzymes present in hepatocytes which are released into the blood of patients as a consequence of hepatocyte damage. Extremely high values, where transaminases are recorded in the thousands, occur in acute liver disease, for example, viral hepatitis or paracetamol overdose. In chronic hepatitis, serum transaminases are rarely more than five to eight times the normal upper limit. Alkaline phosphatase is present in the canalicular and sinusoidal membranes of the liver but is also present in other sites, especially bone. Concomitant elevation of the enzyme γ-glutamyl transpeptidase confirms the hepatic origin of an elevated alkaline phosphatase. The serum alkaline phosphatase activity may be raised by up to four to six times the normal limit in intrahepatic or extra-hepatic cholestasis. It can also be raised in conditions associated with liver infiltration, such as metastases.

Bilirubin is commonly elevated in hepatocellular pathology and especially in acute hepatitis and end-stage chronic disease. An increase in bilirubin concentration results in jaundice and is usually clinically apparent when the serum bilirubin level exceeds 50 μmol/L. In acute liver disease, the serum bilirubin reflects severity of disease but is of little prognostic value. In chronic liver disease, a gradual increase for no apparent reason usually reflects serious disease progression. Hepatocellular damage, cholestasis and haemolysis can all cause elevations in the serum bilirubin concentration.

Synthetic function capacity is very important in assessing liver disease. Prothrombin time (PT), international normalised ratio (INR) and other coagulation studies are useful short-term markers of the synthetic function, especially in acute liver insults where they reflect the severity of the liver injury. PT or INR are also important indicators of chronic liver disease when combined with albumin levels. Albumin is synthesised in the liver and serum albumin levels reflect liver function over the preceeding months rather than days as with coagulation studies. Alternative causes of hypoalbuminaemia need to be considered, especially proteinuria.

Laboratory investigation of aetiology

All individuals presenting with derangement of liver function should be tested for hepatitis A, B, and C as part of a routine liver disease screen. Auto-antibodies and immunoglobulins to screen for autoimmune disease are also relevant to both acute and chronic liver disease. Serum ferritin, caeruloplasmin (in patients under 40 years), α_1-antitrypsin phenotype and lipid profile are standard investigations in patients with evidence of chronic liver disease.

Imaging techniques

Ultrasound is a non-invasive, low-risk procedure that is pivotal in the preliminary assessment of liver disease as it assesses the size, shape and texture of the liver and screens for dilatation of the biliary tract. In patients with chronic liver disease, it assesses patency of the portal vein and may detect signs of portal hypertension (increased spleen size, ascites). It is also routinely used to screen for hepatocellular carcinoma and other hepatobiliary malignancies. Computed tomography (CT) and magnetic resonance (MR) scans are regularly used for more precise definition of any abnormalities identified on ultrasound.

Liver biopsy

Liver biopsy is an invasive procedure with an associated morbidity and mortality, albeit extremely low. Nevertheless, it remains the gold standard in establishing a diagnosis and assessing the severity of chronic liver disease. Progress has been made in developing techniques to assess liver fibrosis non-invasively and a technique called Fibroscan appears to be effective in patients with HCV. In some instances, liver histology will contribute to the decision-making process with regard to therapy, for example, whether to initiate antiviral therapy for HBV or HCV. In acute hepatic dysfunction, a liver biopsy is usually unnecessary, especially if the condition is self-limiting.

Patient care

Pruritus

Pruritus is a prominent and sometimes distressing symptom of chronic liver disease and tends to be most debilitating in the context of cholestatic conditions. The pathogenesis of pruritus in liver disease is poorly understood but the deposition of bile salts within the skin is considered to be central to its development. However, the concentration of bile salts in the skin does not appear to correlate with the intensity of pruritus. Management of pruritus is variable. Relief of biliary obstruction by endoscopic, radiological or surgical means is indicated in patients with obstructed biliary systems. In other cases, pharmacological agents are used initially but in some cases plasmapheresis, molecular absorbants recirculating system (MARS) or even liver transplantation may be needed.

Anion exchange resins

Colestyramine and colestipol act by binding bile acids and preventing their reabsorption. These anion exchange resins are the first line of therapy in the treatment of pruritus. Colestyramine is usually initiated at a dosage of 4 g once or twice daily, and the dose is then titrated to optimise relief without causing side effects (predominantly gastro-intestinal). Such adverse effects are common and include constipation, diarrhoea, fat and vitamin malabsorption. Palatability is variable and consequently adherence is often a problem. In order to enhance compliance, patients should be advised that the benefits of therapy may take time to become apparent and often up to a week. Anion exchange resins can reduce the absorption of concomitant therapy and such drugs should be taken 1 h prior to or 4 h after colestyramine or colestipol ingestion. Drugs which are susceptible to this interaction include digoxin, thyroxine, ursodeoxycholic acid (UDCA), chlorothiazide, propranolol and the antibiotics tetracycline and penicillin.

Antihistamines

Although frequently used, antihistamines are usually ineffective in the management of the pruritus caused by cholestasis and should not be considered first-line therapy. A non-sedating antihistamine such as cetirizine (10 mg once daily) or loratidine (10 mg once daily) is preferred as these avoid precipitating or masking encephalopathy. Antihistamines such as chlorphenamine or hydroxyzine provide little more than sedative properties, although they may be useful at night if the severity of pruritus is sufficient to prevent a patient from sleeping.

Ursodeoxycholic acid

The bile acid UDCA (10 mg/kg daily in two divided doses) has been used frequently in cholestatic liver disease and long-term use has been shown to be effective in the treatment of pruritus. However, in about 5% of cases it worsens the pruritus.

Rifampicin

Rifampicin induces hepatic microsomal enzymes, which may benefit some patients, possibly by improving bile flow. Rifampicin, administered at a dose of 600 mg/day may be effective in the treatment of pruritus, albeit over a more prolonged period of time (1–3 weeks). It is most commonly used in patients with PBC. Its use is restricted by its potential hepatotoxicity and drug interactions with other agents.

Opioid antagonists

A growing spectrum of opioid antagonists have been used to treat pruritus because it is believed that endogenous opioids in the central nervous system are potent mediators of itch. As a consequence the centrally acting opioid antagonists naloxone, naltrexone and nalmefene are thought to reverse the actions of these endogenous opioids. The use of such agents is limited by their route of administration. Naloxone is given by subcutaneous injection, while naltrexone and nalmefene are reported to be more substantially bioavailable after oral administration. A summary of drugs used in the management of pruritus is shown in Table 16.2.

Table 16.2 Drugs commonly used in the management of pruritus

Drug	Indication	Daily dose	Advantage	Disadvantage
Colestyramine	Cholestatic jaundice Itching (first line)	4–16 g (in two or three divided doses)	Reduce systemic bile salt levels	Poor patient adherence due to unpalatability Diarrhoea/constipation Increased flatulence Abdominal discomfort
Ursodeoxycholic acid	Cholestatic jaundice Itching	10–15 mg/kg (in two divided doses)		Variable response
Menthol 2% in aqueous cream	Itching	As required	Local cooling effect	Variable response
Chlorphenamine	Itching	4–16 mg (in three or four divided doses)	Sedative effects may be useful for night-time itching	May precipitate/aggravate encephalopathy
Hydroxyzine	Itching	25–100 mg (in three or four divided doses)	Sedative effects may be useful for night-time itching	May precipitate/aggravate encephalopathy
Cetirizine	Itching	10 mg (once daily)	Antihistamine with low incidence of sedation	Variable response
Naltrexone	Itching	50 mg/day	Shown to be beneficial in primary biliary cirrhosis	Opiate withdrawal symptoms, usually transient

Topical preparations

Topical therapy may benefit some patients. Calamine lotion or menthol 2% in aqueous cream are standard preparations, but improvement of pruritus with such agents is variable.

Clotting abnormalities

The relationship of liver disease to clotting abnormalities is shown diagrammatically in Fig. 16.5. Haemostatic abnormalities develop in approximately 75% of patients with chronic liver disease and 100% of patients with ALF. The majority of clotting factors (with the exception of factor V) are dependent on vitamin K. Patients with liver disease who develop deranged blood clotting should receive intravenous doses of phytomenadione (vitamin K), usually 10 mg daily for 3 days. Administration of vitamin K to patients with significant liver disease does not usually improve the prothrombin time because the liver is unable to utilise the vitamin to synthesis clotting factors. Oral vitamin K is less effective than the parenteral form and so, has little or no place in the management of clotting abnormalities and bleeding secondary to liver disease.

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants should be avoided in all patients with liver disease because of the risk of altering platelet function, causing gastric ulceration and bleeding. NSAIDs have also been implicated in precipitating renal dysfunction and variceal bleeding in patients with end-stage liver disease. Although COX-2 inhibitors may cause a lower incidence of bleeding complications, currently they are avoided in patients with liver disease as their use still poses a risk.

Ascites

The aim in the treatment of ascites is to mobilise the abnormal collection of third space fluid (intra-abdominal fluid) and this can be achieved by simple measures such as reduced sodium intake. A low-salt diet (60–90 mEq/day) may be enough to facilitate the elimination of ascites and delay reaccumulation of fluid. Salt reduction combined with fluid restriction (approximately 1–1.5 L/day) are practical measures taken to mobilise fluid and provide weight reduction and symptomatic relief.

Aggressive weight reduction in the absence of peripheral oedema should be avoided as it is likely to lead to intravascular fluid depletion and renal failure. Weight loss should not exceed 300–500 g/day in the absence of peripheral oedema and 800–1000 g/day in those with peripheral oedema to prevent renal failure. However, diuretics and/or paracentesis are the cornerstone in the management of moderate to large volume ascites. A sequential approach to the management of ascites is outlined in Box 16.1.

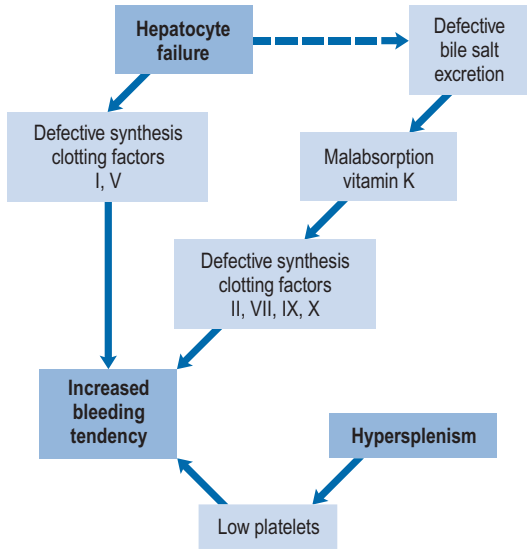

Fig. 16.5 Mechanisms of deranged clotting in chronic liver disease.

Diuretics

The aldosterone antagonist, spironolactone is usually used as a first-line agent in the treatment of ascites. In most instances, a negative sodium balance and loss of ascitic fluid can be achieved with low doses of diuretics. Spironolactone can be used alone or in combination with a more potent loop diuretic. The specific agents and dosages used are outlined in Table 16.3. Spironolactone acts by blocking sodium reabsorption in the collecting tubules of the kidney. It is usually commenced at 50–100 mg/day, but this varies, depending on the patient's clinical status, electrolyte levels and concomitant drug therapies. It can take many days to have a therapeutic effect, so dose augmentation should be conducted with caution and strict observation of renal parameters. The addition of a loop diuretic, furosemide 40 mg/day enhances the natriuretic activity of spironolactone, and should be used when ascites is severe or when spironolactone alone fails to produce acceptable diuresis.

The use of more potent diuretic combinations may result in excessive diuresis which can lead to renal failure of pre-renal origin. The initiation and augmentation of diuretic therapy should ideally be carried out in hospital. This allows strict urea and electrolyte monitoring to detect impending hyperkalaemia and/or hyponatraemia, which commonly occur with diuretic therapy. It also allows the

Box 16.1 The sequential approach to the management of cirrhotic ascites

Bedrest and sodium restriction (60–90 mEq/day, equivalent to 1500–2000 mg of salt/day)
▼
Spironolactone (or other potassium-sparing diuretic)
▼
Spironolactone and loop diuretic
▼
Large-volume paracentesis and colloid replacement

Other measures
Transjugular intrahepatic portosystemic shunt (TIPS)
Peritonovenous shunt
Consider orthotopic liver transplantation

Table 16.3 Diuretics used in the management of ascites

Drug	Indication	Daily dose	Advantage	Disadvantage
Spironolactone	Fluid retention	50–400 mg	Aldosterone antagonist Slow diuresis	Painful gynaecomastia Variable bioavailability Hyperkalaemia
Furosemide	Fluid retention	40–160 mg	Rapid diuresis Sodium excretion	Nephrotoxic Hypovolaemia Hypokalaemia Hyponatraemia Caution in pre-renal uraemia
Amiloride	Mild fluid retention	5–10 mg	As K^+-sparing agent or weak diuretic if spironolactone contraindicated	Lacks potency

baseline measurement of urinary sodium excretion, subsequent changes in the diuretic dose should be titrated against urinary sodium excretion. Aggressive and unchecked diuresis will precipitate the hepatorenal syndrome, which has a very poor prognosis. Generally, if the serum sodium level decreases to less than 130 mmol/L or if creatinine levels rise to greater than 130 µmol/L then dose escalation of diuretics should be stopped. Diuretic therapy can be complicated by encephalopathy, hypokalaemia, hyponatraemia and azotaemia. Gynaecomastia and muscle cramps are side effects of diuretic therapy.

Refractory ascites, which occurs in 5–10% of patients with ascites, is associated with a 1-year survival rate of 25–50%. Therapeutic strategies include repeated large volume paracentesis combined with the administration of plasma expanders or alternatively, TIPS. In some patients, liver transplantation may be indicated. Ascites is considered to be refractory or diuretic resistant if there is no response with once daily doses of 400 mg spironolactone and 160 mg furosemide. Again, urinary sodium excretion provides important information in terms of the response to or viability of dose augmentation with diuretic therapy. Patients on lower doses of diuretics are also considered to have refractory ascites if side effects are a problem, for example, hepatic encephalopathy, hyperkalaemia, hyponatraemia or azotemia.

Paracentesis

Repeated large volume paracentesis in combination with albumin administration is the most widely accepted therapy for refractory ascites. Patients generally require paracentesis every 2–4 weeks and the procedure is often performed in the outpatient setting. Paracentesis, however, does not affect the mechanism responsible for ascitic fluid accumulation and so early recurrence is common. Intravenous colloid replacement or plasma expanders are used to prevent adverse effects on the renal and systemic circulation. Colloid replacement in the form of 6–8 g albumin/L of ascites removed (equivalent to 100 mL of 20% human albumin solution [1 unit] for every 2.5 L of ascitic fluid removed) is a standard regimen.

Transjugular intrahepatic portosystemic shunting (TIPS)

TIPS is an invasive procedure, used to manage refractory ascites or control refractory variceal bleeding. It is carried out under radiological guidance. An expandable intrahepatic stent is placed between one hepatic vein and the portal vein by a transjugular approach (Fig. 16.6). In contrast to paracentesis, the use of TIPS is effective in preventing recurrence in patients with refractory ascites. It reduces the activity of sodium retaining mechanisms and improves the renal response to diuretics. However, a disadvantage of this procedure is the high rate of shunt stenosis (up to 30% after 6–12 months) which leads to recurrence of ascites. TIPS can also induce or exacerbate hepatic encephalopathy.

Spontaneous bacterial peritonitis (SBP)

Patients with ascites should be closely observed for SBP as it develops in 10–30% of patients and has a high mortality. Hepatorenal syndrome can complicate SBP in up to 30% of

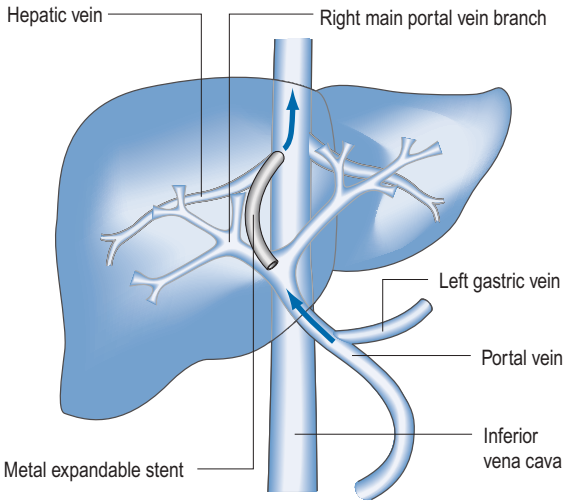

Fig. 16.6 Intrahepatic stent shunt links the hepatic vein with the intraheptic portal vein.

patients and also carries a high mortality. Conventional signs and symptoms of peritonitis are rarely present in such patients and if suspected, treatment with appropriate antibiotics should be started immediately after a diagnostic ascitic tap has been taken. A polymorphonuclear leucocyte count of greater than 250 cells/mm^3 is diagnostic of this condition. The causative organism is of enteric origin in approximately three-quarters of infections, and originates from the skin in the remaining one-quarter. Cefotaxime (2 g, 8 hourly) is effective in 85% of patients with SBP and is commonly used as first-line antimicrobial therapy. Other antibiotic regimens have been used including co-amoxiclav, but third-generation cephalosporins are the treatment of choice. The quinolone, norfloxacin (400 mg/day), has a role in the prevention of recurrence of SBP, estimated as 70% at 1-year, and is recommended for long-term antibiotic prophylaxis. However, the emergence of quinolone-resistant bacteria is a growing problem in the management of SBP.

Hepatic encephalopathy

Hepatic encephalopathy is a reversible neuropsychiatric complication that occurs with significant liver dysfunction. The precise cause of encephalopathy remains unclear, but three factors are known to be implicated, namely portosystemic shunting, metabolic dysfunction and an alteration of the blood–brain barrier. It is thought that intestinally derived neuroactive and neurotoxic substances such as ammonia pass through the diseased liver or bypass the liver through shunts and go directly to the brain. This results in cerebral dysfunction. Ammonia is thought to increase the permeability of the blood–brain barrier, enabling other neurotoxins to enter the brain, and indirectly alter neurotransmission. Other substances implicated in causing hepatic encephalopathy include free fatty acids, γ-aminobutyric acid (GABA) and glutamate.

Clinical features of hepatic encephalopathy range from trivial lack of awareness, altered mental state to asterixis (liver flap) through to gross disorientation and coma. During low-grade encephalopathy, the altered mental state may present as impaired judgement, altered personality, euphoria or anxiety. Reversal of day/night sleep patterns is very typical of encephalopathy. Somnolence, semistupor, confusion and, finally, coma can ensue (Table 16.4).

Encephalopathy associated with cirrhosis and/or portal-systemic shunts may develop as a result of specific precipitating factors (Box 16.2) or spontaneously. Common precipitating factors include gastro-intestinal bleeding, SBP, constipation, dehydration, electrolyte abnormalities and certain drugs including narcotics and sedatives. Identification and removal of such precipitating factors is mandatory. Therapeutic management is then aimed at reducing the amount of ammonia or nitrogenous products in the circulatory system. Treatment with laxatives increases the throughput of bowel contents, by reducing transit time and also increases soluble nitrogen output in the faeces. Drug therapies for encephalopathy are summarised in Table 16.5.

Lactulose, a non-absorbable disaccharide, decreases ammonia production in the gut. It is widely used as it is broken down by gastro-intestinal bacteria to form lactic, acetic and formic acids. The effect of lactulose is to acidify the colonic contents which leads to the ionisation of nitrogenous products within the bowel, with a consequent reduction in their absorption from the gastro-intestinal tract. Lactulose is commenced in doses of 30–40 mL/day and titrated to result in two to three bowel motions each day. Patients unable to take oral medication or those with worsening encephalopathy are treated with phosphate enemas.

Antibiotics such as metronidazole or neomycin may also be used to reduce ammonia production from gastro-intestinal bacteria. Metronidazole has been the preferred option in the past, while the use of neomycin has largely been abandoned because of associated toxicity. Recent data has supported the use of the rifaximin, a minimally absorbed antibiotic, for the treatment of acute encephalopathy and the remission of chronic encephalopathy (Bass et al., 2010). Other therapies investigated for the treatment of encephalopathy include L-ornithine-L-aspartate (LOLA), sodium benzoate, L-dopa, bromocriptine and the benzodiazepine receptor antagonist, flumazenil.

Table 16.4 Grading of hepatic encephalopathy

Grade 0	Normal
Subclinical	Abnormal psychometric tests for encephalopathy (e.g. number correction test)
Grade 1	Mood disturbance, abnormal sleep pattern, impaired handwriting +/− asterixis
Grade 2	Drowsiness, grossly impaired calculation ability, asterixis
Grade 3	Confusion, disorientation, somnolent but arousable, asterixis
Grade 4	Stupor to deep coma, unresponsive to painful stimuli

Box 16.2 Precipitating causes of hepatic encephalopathy

- Gastro-intestinal bleeding
- Infection (spontaneous bacterial peritonitis, other sites of sepsis)
- Hypokalaemia, metabolic alkalosis
- High protein diet
- Constipation
- Drugs, opioids and benzodiazepines
- Deterioration of liver function
- Post-surgical TIPS

Oesophageal varices

Variceal bleeding is the most feared complication of portal hypertension in patients with cirrhosis and there is a 30% lifetime risk of at least one bleeding episode among patients with cirrhosis and varices. Treatment of variceal bleeding includes

Table 16.5 Drugs commonly used in the management of encephalopathy

Drug	Dose	Comment	Side effects
Lactulose	15–30 mL orally 2–4 times daily	Aim for 2–3 soft stools daily	Bloating, diarrhoea
Metronidazole	400–800 mg orally daily in divided doses	Metabolism impaired in liver disease	Gastro-intestinal disturbance
Neomycin Used less frequently now	2–4 g orally daily in divided doses	Maximum duration of 48 h	Potential for nephro- and ototoxicity
Rifaxamin	550 mg twice daily	Benefit demonstrated over 6 months use	Allergic reactions, gastro-intestinal disturbance May permit overgrowth *Clostridium difficile*

endoscopic banding, or rarely sclerotherapy, of oesophageal varices in parallel with splanchnic vasoconsrictors and intensive medical care. Patients with variceal bleeding refractory to endoscopic intervention or patients bleeding from ectopic or uncontrolled gastric varices will need TIPS or surgical decompressive shunts. Refractory variceal bleeding should, therefore, be managed in centres with the appropriate expertise.

Initial treatment is aimed at stopping or reducing the immediate blood loss, treating hypovolaemic shock, if present, and subsequent prevention of recurrent bleeding. Immediate and prompt resuscitation is an essential part of treatment. Only when medical treatment has been initiated and optimised should endoscopy be performed. Endoscopy confirms the diagnosis and allows therapeutic intervention. Fluid replacement is invariably required, and should be in the form of colloid or packed red cells and administered centrally. Saline should generally be avoided in all patients with cirrhosis. Fluid replacement must be administered with caution, as overzealous expansion of the circulating volume may precipitate further bleeding by raising portal pressure, thereby exacerbating the clinical situation. A flow chart for the management of bleeding oesophageal varices is shown in Fig. 16.7.

Endoscopic management

Variceal band ligation uses prestretched rubber bands applied to the base of a varix which has been sucked into the banding chamber attached to the front of an endoscope. Variceal

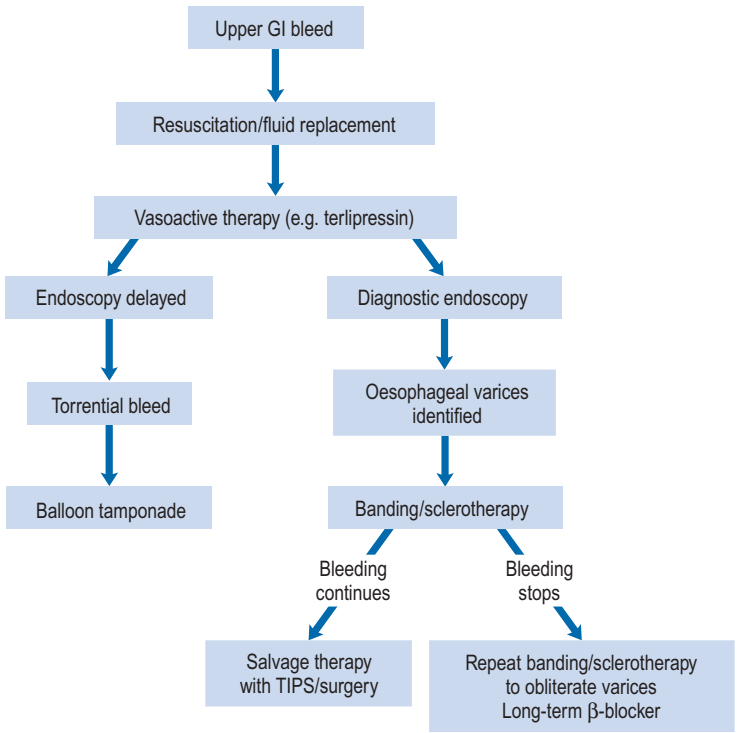

Fig. 16.7 Management of oesophageal variceal haemorrhage.

band ligation (VBL) controls bleeding in approximately 90% of cases. It is at least as effective as sclerotherapy, which it has largely superceded, and is associated with fewer side effects. Balloon tamponade with a Sengstaken–Blakemore balloon or Linton balloon may be used to stabilise a patient with actively bleeding varices by directly compressing the bleeding varices, until more definitive therapy can be undertaken. Balloon tamponade can control bleeding in up to 90% of cases but 50% rebleed when the balloon is deflated. Gastric varices develop in approximately 20% of patients with portal hypertension. The risk of gastric variceal bleeding is lower than that of oesophageal variceal bleeding, but bleeding from fundal varices is more difficult to manage and is associated with a higher mortality. The most effective treatment strategy for fundal varices is now considered to be variceal obturation with tissue adhesives or 'glue injection'. The use of cyanoacrylate injection in the treatment of fundal varices is associated with less rebleeding and is emerging as the treatment of choice in the hands of experienced endoscopists.

Drug treatment

Several pharmacological agents are available for the emergency control of variceal bleeding (Table 16.6). Most act by lowering portal venous pressure. They are generally used to control bleeding in addition to balloon tamponade and emergency endoscopic techniques. Vasopressin was the first vasoconstrictor used to reduce portal pressure in patients with actively bleeding varices. However, its associated systemic vasoconstrictive adverse effects limited its use. The synthetic vasopressin analogue, terlipressin, is highly effective in controlling bleeding and in reducing mortality. It can be administered in bolus doses every 4–6 h and has a longer biological activity and a more favourable side effect profile. Once a diagnosis of variceal bleeding has been established, a vasoactive drug infusion (usually terlipressin) should be started without further delay and continued for 2–5 days. Somatostatin and the somatostatin analogue, octreotide, are reported to cause selective splanchnic vasoconstriction and reduce portal pressure. Although they are reported to cause less adverse effects on the systemic circulation, terlipressin remains the agent of choice.

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS is now established as the preferred rescue therapy in cases where endoscopic intervention has failed to control bleeding (Fig. 16.7). Recent data suggests the use of early TIPS, within the first 48 h, may be life saving in patients with advanced liver failure.

Table 16.6 Drugs used in the treatment of acute bleeding varices

Drug	Dosage and administration
Terlipressin	1–2 mg bolus 4–6 hourly for 48 h
Octreotide	50 µcg/h i.v. infusion for 48 h or longer if patient rebleeds

Prevention of rebleeding

Endoscopic band ligation (EBL) is performed at regular intervals (1–2 weeks) as part of an eradication programme to obliterate the varices. Once varices have been eradicated, endoscopic follow-up can be performed less frequently (3 monthly) for the first year, then twice yearly thereafter. If varices reappear they should be banded regularly until eradicated again. Non-selective β-blockers, such as propranolol, are the medication of choice to prevent rebleeding and can also be used as primary prophlaxis against variceal bleeding in patients with known varices. The mechanism of action is complex, but they reduce portal hypertension by causing splanchnic vasoconstriction and reduced portal blood flow. At higher doses they can have a more marked negative effect on cardiac output and so must be titrated accordingly.

Acute liver failure

ALF occurs when there is a rapid deterioration in liver function in previously healthy individuals resulting in encephalopathy and a coagulopathy. ALF is a multisystem disorder with cerebral oedema and renal impairment being particularly important complications. In the past, viral hepatitis was a major consideration in the aetiology of ALF. However, the development of a commercial vaccine for hepatitis B has seen a dramatic decline in the contribution of HBV to ALF in Western countries. The most common cause of ALF in the UK and USA is paracetamol (acetaminophen) toxicity. Seronegative hepatitis is the other common aetiological group. Management of ALF is complicated, involving supporting the central nervous system, cardiovascular and renal systems. All patients with ALF are at risk of infection, and prophylactic administration of broad spectrum antibiotics and antifungal agents is standard practice. Coagulopathy and bleeding resulting from liver failure are well-recognised life-threatening complications which require specialised monitoring and early correction.

Liver transplantation

Liver transplantation is the established treatment for selected patients with ALF, decompensated chronic liver disease, inherited metabolic disorders and primary liver cancer. HCV and alcohol-induced end-stage liver disease are the commonest indications for liver transplantation in Europe and the USA. Typical 1 year survival rates are around 90% for elective transplants. Remarkably few transplants fail because of rejection and, nowadays, technical problems, infection and multisystem failure account for most deaths in the first year. Recurrence of the primary disease, malignancy and death with a functioning graft account for most late deaths.

An increasing number of immunosuppressive agents are now available and this has enabled clinicians to tailor immunosuppression to achieve a balance of good graft function

and an acceptable side effect profile. The calcineurin inhibitors (CNIs), tacrolimus and ciclosporin remain the mainstay of immunosuppressive therapy. Corticosteroids are still commonly used, at least during the first 3 months after transplantation. The other drugs used regularly for long-term immunosuppression include azathioprine, mycophenolate, sirolimus and everolimus. Therapy is monitored closely and increasingly tailored to individual patients, with a particular emphasis on preserving renal function and reducing the risk of cardiovascular disease.

Disease specific therapies

Hepatitis B

The primary goal in the management of chronic HBV infection is to prevent cirrhosis, hepatic failure and hepatocellular carcinoma. The ideal outcome is eradication of HBV with HBsAg loss and the prevention of irreversible liver damage. However, the eradication of HBV is near impossible because of the presence of extra-hepatic reservoirs of HBV and the integration of HBV into the host genome and the presence of an intracellular conversion pathway which replenishes the pool of transcriptional templates in the hepatocyte nucleus without the need for reinfection. For this reason, the main treatment goal is continuous viral suppression and current therapies, specifically with oral antiviral agents, are judged by their ability to provide continuous viral suppression.

It is the persistence of covalently closed circular DNA (cccDNA) which is considered to preclude a 'cure' for HBV. Thus, therapies currently available for the treatment of chronic HBV are measured in terms of HBeAg seroconversion (in eAg positive disease), viral suppression, ALT normalisation and improvement in liver histopathology. More recently, there has been specific focus on HBsAg quantification, with loss of HBsAg considered a surrogate marker of cccDNA levels (Sung et al., 2005). Thus, all therapies in the treatment of HBV should be benchmarked against HBsAg loss, as a marker of drug utility and efficacy.

There is now concensus amongst the major liver disease authorities in terms of their clinical practice guidelines and the recommended agents available for the treatment of chronic HBV infection. Treatment strategies have broadened and include the potent oral antiviral agents tenofovir (Marcellin et al., 2008; National Institute for Health and Clinical Excellence, 2009) and entecavir (National Institute for Health and Clinical Excellence, 2008) as first-line monotherapies. While these two agents have emerged as the leading oral antivirals, the weaker and more outdated agents such as telbivudine, lamivudine and adefovir are still widely used. The use of lamivudine or adefovir as monotherapy is no longer recommended and should be avoided if at all possible, owing to the high rates of resistance reported with these drugs. Pegylated interferon (peginterferon) alfa-2a has re-emerged as a viable alternative to oral antiviral agents in the treatment of chronic HBV. This is due primarily to its potent immunomodulatory effects which gives it a clear advantage over oral antivirals. Significant rates of surface antigen (sAg) loss have been reported in both HBeAg positive and negative disease and the inclusion of surface antigen quantification has provided an objective tool to assess response to pegylated interferon. The advantages of interferon therapy, such as a finite treatment course, good rates of surface antigen loss in selected patients, must be weighed against the disadvantages associated with an injection-based therapy and the inherent side effect profile associated with interferons. Therefore, a careful and rational approach must be followed when considering treatment of chronic HBV. While reported rates of resistance is extremely low with entecavir, and none reported with tenofovir, the treatment landscape for chronic HBV has changed dramatically from the high rates of resistance previously seen with lamivudine and adefovir. However, when commencing oral antiviral agents, the patient must be aware they are potentially embarking on a lifelong course of treatment.

An issue which must be given further consideration is the potential side effect profile of these relatively new drugs, notwithstanding their potency and documented efficacy. The potential for unforeseen side effects must be considered unresolved, as safety data to date are limited by the relatively short period of time that these drugs have been used in clinical practice. Likewise, physicians will need to remain vigilant for the emergence of resistant virus, even with these potent agents with well-described high-genetic barriers to resistance.

Hepatitis C

The primary aim of treating patients with chronic HCV is viral clearance with sustained virologic response (SVR) defined as the absence of viraemia 6 months after antiviral therapy has been discontinued. Viral clearance improves the patient's quality of life and reduces the risk of progression to cirrhosis and hepatocellular carcinoma.

Pegylated interferon and ribavirin combination therapy are now the standard care of chronic HCV (National Institute for Health and Clinical Excellence, 2010). The SVR for treatment of naïve patients is of the order of 55% for genotypes 1 and 4 (48 weeks of therapy) and 80–85% for genotypes 2 and 3 (24 weeks of therapy). The treatment duration, however, can be individualised based on the baseline viral load and the speed of virological response during treatment. Patients failing to achieve a significant reduction in viral load after 12 weeks will normally have therapy discontinued. The current standard of care combination therapy is limited by the side effect profile, complications of therapy and poor patient tolerability. Side effects of therapy include influenza-like symptoms, decrease in haematological parameters (haemoglobin, neutrophils, white blood cell count and platelets), gastrointestinal complaints, psychiatric disturbances (anxiety and depression) and hypo- or hyperthyrodism. It is accepted that these side effects are a major obstacle preventing completion of therapy by hindering compliance or enforcing significant dose reductions. While growth factors (erythropoietin, GCSF) and antidepressants may alleviate some side effects,

there remains a clear need for better treatment strategies in chronic HCV infection.

Significant progress has been made in the development of new HCV-specific inhibitors. Data from recent trials have shown a marked improvement in SVR when these new protease inhibitors, telaprevir and boceprevir are given in combination with current standard of care, increasing response rates to 61–75% in genotype 1 HCV infection. It is anticipated that these agents will be available for clinical practice from 2011. Several new HCV-specific inhibitors are currently in clinical evaluation including protease inhibitors, nucleoside and non-nucleoside polymerase inhibitors as well as non-HCV compounds with anti-HCV activity. It is envisaged, as a result of this evolution of HCV therapies, that the treatment options for HCV will become more robust.

Autoimmune hepatitis

Corticosteroids and/or azathioprine are the standard therapy for AIH. Prednisone or prednisolone are administered at doses of 40–60 mg/day alone or at lower doses when combined with azathioprine. The steroid dose is reduced over a 6-week to 3-month period to a target maintenance dose of 7.5 mg/day or lower. The disturbance in aminotransferases usually normalises within 6–12 weeks, but histological remission tends to lag by 6–12 months. Azathioprine at a dose of 1–1.5 mg/kg/day is used as an adjunct to corticosteroid therapy. Azathioprine, used alone, is ineffective in treating the acute phase of AIH. In patients intolerant of azathioprine, or in cases of proven treatment failure, other immunosuppressants have been used, for example, tacrolimus and mycophenolate. Newer corticosteroids such as budesonide, with fewer systemic side effects, have also been used effectively and may have a greater role in the future treatment of AIH.

Primary biliary cirrhosis. Several therapies have been associated with short-term symptomatic improvements in liver function tests. UDCA, the only medication widely used to treat PBC, reduces the retention of bile acids and increases their hepatic excretion. Therefore, it is effective in protecting against the cytotoxic effects of dihydroxy bile acids which accumulate in PBC. However, UDCA does not appear to prevent ongoing bile duct injury and disease progression. Therefore, liver transplantation remains the only effective option in patients with end-stage disease. Immunosuppressive agents such as ciclosporin, azathioprine and methotrexate have also been assessed for the treatment of PBC but clinically significant adverse events outweigh the potential benefits.

Primary sclerosing cholangitis

There is no effective treatment for this condition. UDCA can be used to manage associated cholestasis, and doses as high as 15 mg/kg/day have been advocated despite the limited evidence that it alters the natural history of the disease. Studies with various immunosuppressive agents have been disappointing and transplantation remains the only effective treatment option in patients with advanced disease.

Wilson's disease

This rare autosomal recessive condition is usually managed with chelation therapy. Penicillamine is the agent of choice in Wilson's disease as it promotes urinary copper excretion in affected patients and prevents copper accumulation in presymptomatic individuals. Initial treatment of 1.5–2 g/day is given in divided doses. Initially, neurological symptoms may worsen because of deposition of mobilised copper in the basal ganglia, but symptomatic patients tend to improve over a period of several weeks. Other therapy-related adverse effects include renal dysfunction, haematological abnormalities and disseminated lupus erythematosis. Therefore, regular monitoring of full blood count and electrolytes is required as well as small doses of pyridoxine (25 mg) to counteract the antipyridoxine effect of penicillamine and the associated neurological toxicity. Patients unable to tolerate penicillamine may respond to trientine. This chelating agent is less potent than penicillamine but has fewer adverse effects. Oral zinc is also used but it too is less potent than penicillamine.

Case studies

Case 16.1

A 56-year-old man is admitted to hospital following haematemesis and melaena. He has a known history of alcoholic liver disease (stopped drinking alcohol 1 year ago) with marked ascites.
A provisional diagnosis of bleeding oesophageal varices is made.

A Sengstaken–Blakemore tube is inserted and the balloon inflated as a temporary measure to arrest bleeding. The patient is transferred 8 h later to a specialist regional centre for further management.

Laboratory data on admission are:

Na	**124 (133–143 mmol/L)**
K	**3.0 (3.5–5.0 mmol/L)**
Creatinine	**131 (80–124 µmol/L)**
Urea	**14.3 (2.7–7.7 mmol/L)**
Bilirubin	**167 (3.15 µmol/L)**
ALT	**24 (0–35 IU/L)**
PT	**18.9 (13 s)**
Albumin	**24 (35–50 g/dL)**
Hb	**8.9 (13.5–18 g/dL)**

Drugs on admission:

Spironolactone 200 mg one each morning.

Questions

1. What other action would you have recommended before the patient was transferred to the regional centre?
2. What options (drug and/or non-drug) are likely to be available at the regional centre for managing the patient's bleeding varices?
3. What further long-term measures would you recommend for this patient?

Answers

1. Initial restoration of circulating blood volume with colloid, followed by cross-matched blood. Fluid replacement is necessary to protect renal perfusion. In view of the patient's ascites, saline should be avoided. Dextrose 5% with added

potassium (hypokalaemia present) would be a reasonable choice. A pharmacological agent to reduce portal pressure, such as terlipressin 1–2 mg every 4–6 h or octreotide 50 µcg/h, should be started. Current evidence supports terlipressin over octreotide. Broad spectrum antibiotics such as cefuroxime and metronidazole should be started intravenously if there is suspicion of abdominal infection or sepsis. There is no evidence that gastric acid suppression is beneficial, but if the bleeding is caused by a gastric mucosal lesion, a proton pump inhibitor such as lansoprazole or omeprazole, or a histamine type-2 receptor antagonist such as ranitidine can be administered.

Spironolactone is likely to be either causing or exacerbating the low sodium and should be discontinued.

Vitamin K, 10 mg intravenously once daily for 3 days, should be administered to try to correct the raised prothrombin time. As the patient has severe liver disease with varices and ascites there is a possibility he may develop encephalopathy. It would be advisable to start lactulose or, if the patient is unable to take medicines orally, administer an enema such as a phosphate enema.

2. *Banding/ligation*: this has a similar efficacy to sclerotherapy but fewer complications. It involves mechanical strangulation of variceal channels by small elastic plastic rings mounted on the tip of the endoscope.

   Transjugular intrahepatic portosystemic shunt (TIPS): this can be used to reduce portal pressure, but there is a risk of precipitating encephalopathy.

   Banding is the first-line option for managing bleeding oesophageal varices. Patients who continue to bleed after two endoscopic treatments should be considered for TIPS. Surgery involving portal-systemic shunts or devascularisation are possible options if the above alternatives repeatedly fail. Extra-hepatic portal-systemic shunts are situated outside the liver and divert portal blood flow into the systemic circulation bypassing the liver. Devascularisation involves obliteration of the collateral vessels supplying blood to the varices.
3. Banding/ligation can be performed at regular intervals of 1–2 weeks to obliterate the varices. Once varices have been eradicated, endoscopic follow-up should be undertaken every 3 months for the first year then every 6–12 months thereafter. If varices reappear they should be banded regularly until eradicated again. Non-selective β-blockers such as propranolol are used in the prophylaxis of further bleeds, with the dose adjusted until the heart rate is reduced by 25%, but to not less than 55 beats/min.

Case 16.2

A 68-year-old woman with a long-standing history of alcoholic liver disease is admitted to hospital with a 2-week history of vomiting, confusion, increased abdominal distension and worsening jaundice.
On admission laboratory data are as follows:

Na	**116 (133–143 mmol/L)**
K	**3.8 (3.5–5 mmol/L)**
Urea	**8.5 (3.3–7.7 mmol/L)**
Cr	**119 (80–124 µmol/L)**
Bilirubin	**459 (3–17 µmol/L)**
Albumin	**23 (35–50 g/L)**
ALT	**23 (0–35 iu/L)**
Alk P	**524 (70–300 iu/L)**
PT	**18.6 (13 s)**

Drugs on admission are as follows:

Spironolactone: 300 mg each morning.
Temazepam: 10 mg at night.
Lactulose: 10 mL twice daily.

Questions

Discuss the initial treatment plan for the management of:
1. Ascites
2. Nausea and vomiting
3. Confusion

Answers

From the presenting features and LFTs on admission it is apparent that the patient's liver disease is getting progressively worse, probably as a result of continued alcohol intake. She is confused on admission and this suggests encephalopathy, a common complication of chronic liver disease.

1. *Ascites management.* The patient has increased abdominal distension on admission suggestive of worsening ascites. This might be due to poor adherence with spironolactone, or alternatively, her ascites may have become diuretic resistant.

   The patient should be sodium restricted and confined to bed. Spironolactone therapy should be stopped in view of the low sodium and confusion, as overuse of diuretics can precipitate encephalopathy. Fluid restriction is necessary to reduce the ascites, but sufficient fluid is required to rehydrate the patient following vomiting.

   Paracentesis should be used to manage the ascites. Every litre of ascitic fluid removed should be replaced with 6–8 g of albumin. A diagnostic ascitic tap should be taken to ensure there is no infection in the ascites.
2. *Nausea/vomiting management.* Urea is slightly raised, indicating possible dehydration as a result of vomiting. The patient should be rehydrated with dextrose 5%, not saline, as this will worsen the ascites. Additional potassium should be given to correct the low serum potassium. Note that if the patient has been taking the spironolactone there would normally be an increase in potassium, but in this case the vomiting has probably reduced this. The patient's nausea can be managed with a suitable antiemetic such as domperidone 10 mg four times a day initially and then titrated according to the response.
3. *Confusion.* Confusion may be an early sign of encephalopathy in this patient. Temazepam should be stopped. The patient is on an inadequate dose of lactulose for the management of encephalopathy, so this should be increased to produce 2–3 loose motions per day. A typical dose would be 20 mL three or four times daily. In view of the patient's confusion, it may be worth considering other agents in the management of the encephalopathy, such as metronidazole 400 mg twice daily.

Case 16.3

A 54-year-old woman with primary biliary cirrhosis has been complaining of increasing backache over the last 3 months. Her general condition has deteriorated over the past year during which she has suffered from ascites and encephalopathy. Her main complaint is of continuous back pain, which disturbs her sleep.

Question

How would you manage this patient's back pain?

Answer

Back pain secondary to osteoporosis-related vertebral fractures is common in patients with chronic liver disease, such as primary biliary cirrhosis. This is due to the fact that most patients with

primary biliary cirrhosis are postmenopausal women in their late 50s where bone thinning is likely, secondary to both menopausal and liver changes. Once the diagnosis has been confirmed, the patient should be counselled that the bone pain is chronic, tends to be intermittent, and takes several months to settle after each new fracture. Bed rest is useful in the acute situation, but prolonged bed rest can accelerate bone loss.

Although there have been rapid advances in recent years in the treatment of postmenopausal osteoporosis, very few studies have addressed the problems of treating osteoporosis in patients with chronic liver disease. Hormone replacement therapy has not been evaluated in patients with chronic liver disease, and oestrogen therapy is widely believed to be contraindicated in such patients, although there is little evidence to support this. Transdermal oestrogen preparations that avoid the first-pass metabolic effect may be a possible future option.

The patient should be advised to take adequate calcium supplementation of 1–1.5 g/day in addition to her normal diet. Vitamin D deficiencies are common in chronic liver disease and it would be advisable to administer 300,000 units intramuscularly every 3 months.

For symptomatic management of the pain a variety of analgesics are available. The choice of drug is influenced by both the severity of the pain and the degree of liver impairment.

For mild pain, paracetamol is the mainstay of treatment, and may be used in standard doses in the majority of patients with liver dysfunction. Patients pretreated with cytochrome P450 inducing drugs or patients with a history of alcohol abuse are at increased risk of paracetamol-induced liver injury and should receive only short courses at low doses (maximum of 2 g/day for an adult).

Opioid analgesics should usually be avoided in liver disease because of their sedative properties and the risks of precipitating or masking encephalopathy. If a patient has stable mild to moderate liver disease then short-term use of opioids can be considered. Moderate potency opioids, such as dihydrocodeine and codeine, are eliminated almost entirely by hepatic metabolism. Therapy should be initiated at a low dose, and the dosage interval titrated according to the response of the patient. Despite their low potency, these preparations may still precipitate encephalopathy.

In severe pain, the use of potent opioids is usually unavoidable. They undergo hepatic metabolism, and are therefore likely to accumulate in liver disease. To compensate for this it is important to increase the dosage interval when using these drugs. Morphine, pethidine or diamorphine should be administered at doses at the lower end of the dosage range at intervals of 6–8 h. The patient should be regularly observed and the dose titrated according to patient response. In any patient with liver disease receiving an opioid, it is advisable to coprescribe a laxative as constipation can increase the possibility of developing encephalopathy.

NSAIDs should be avoided in patients with liver disease. All NSAIDs can prolong bleeding time via their effects on platelet function. Impaired liver function itself can lead to a reduced synthesis of clotting factors and an increased bleeding tendency. NSAIDs may also be dangerous due to the increased risk of gastro-intestinal haemorrhage and potential to preciptate renal dysfunction.

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17 Acute kidney injury

P. Cockwell, S. Stringer and J. Marriott

Key points

- Acute renal failure (ARF), or acute kidney injury (AKI), is diagnosed when the excretory function of the kidney declines rapidly over a period of hours or days and is usually associated with the accumulation of metabolic waste products and water.
- A wide range of factors can precipitate AKI, including trauma, obstruction of urine flow or any event that causes a reduction in renal blood flow, including surgery and medical conditions, for example, sepsis, diabetes, acute liver disease, rapidly progressive glomerulonephritis.
- Drug involvement in the development of AKI is common.
- There are no specific signs and symptoms of AKI. The condition is typically indicated by raised blood levels of creatinine and/or a low urine output.
- The clinical priorities in AKI are to manage life-threatening complications, correct intravascular fluid balance and establish the cause of the renal failure, reversing factors causing damage where possible.
- The aim of medical treatment is to remove causative factors and maintain patient well-being so that the kidneys have a chance to recover.
- Most measures of renal function are inaccurate when renal function deteriorates or improves rapidly as is usually the case in AKI.
- Treatment of AKI is essentially supportive, though there are conditions that cause AKI that are reversible with specific treatment.
- AKI is a serious condition with mortality rates up to 70%, varying according to cause and at its highest with concurrent failure of other organs.

Definition and incidence

Acute renal failure (ARF) is a common and serious problem in clinical medicine. It is characterised by an abrupt reduction (usually within a 48-h period) in kidney function. This results in an accumulation of nitrogenous waste products and other toxins. Many patients become oliguric (low urine output) with subsequent salt and water retention. In patients with pre-existing renal impairment, a rapid decline in renal function is termed 'acute on chronic renal failure'. The nomenclature of ARF is evolving and the term acute kidney injury (AKI) is being increasingly used in clinical practice.

The diagnostic criteria for AKI is based on an increase in serum creatinine or the presence of oliguria (see Table 17.1). Criteria have recently been introduced for the definition and staging of the condition; the acronym RIFLE is used (Risk, Injury, Failure, Loss and End-stage renal disease (ESRD)), which is now becoming established in clinical practice (see Fig. 17.1).

The large majority of cases of AKI occur in patients who are already hospitalised for other medical conditions; up to 7% of these sustain AKI and this increases to 30% or more in those who are critically ill. Most cases are caused by pre-renal AKI and are reversed with appropriate intervention. However, severe AKI, as defined by the requirement for dialysis treatment, is often associated with failure of one or more non-renal organs (this is called multi-organ failure); in this setting there is a mortality rate of 70% in patients with sepsis and AKI and 45% in patients without sepsis. AKI that occurs in the community is responsible for around 1% of all hospital admissions.

Classification and causes

AKI is not a single disease state with a uniform aetiology, but a consequence of a range of different diseases and conditions. The most useful practical classification comprises three main groupings: (i) pre-renal, (ii) renal, or (iii) post-renal. More than one category may be present in an individual patient. Common causes of each type of AKI are outlined in Table 17.1.

Table 17.1 Classification of acute kidney injury

Acute kidney injury type	Typical % cases	Common aetiology
Pre-renal	40–80	Reversible ↓ renal perfusion through hypoperfusion
Intra-renal (including ATN)	10–50	Renal parenchymal injury
Post-renal	<10	Urinary tract obstruction

ATN, acute tubular necrosis.

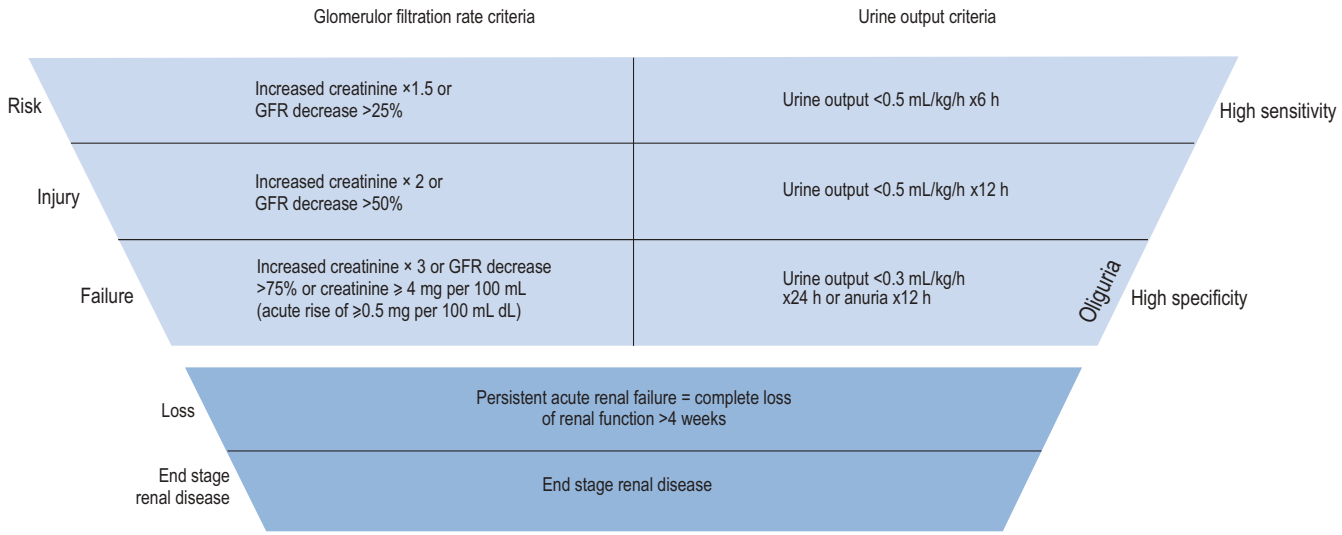


Fig. 17.1 The RIFLE criteria for the definition and staging of acute renal disease.

The kidneys are pre-disposed to haemodynamic injury owing to hypovolaemia or hypoperfusion. This relates to the high blood flow through the kidneys in normal function; the organs represent 5% of total body weight but receive 25% of blood flow. Furthermore, the renal microvascular bed is unique; firstly, the glomerular capillary bed is on the arterial side of the circulation; secondly, the peri-tubular capillaries are down-stream from the glomerular capillary bed. Finally, renal cells are highly specialised and are, therefore, pre-disposed to ischaemic and inflammatory injury.

Pre-renal acute kidney injury

This is caused by impaired perfusion of the kidneys with blood, and is usually a consequence of decreased intravascular volumes (hypovolaemia) and/or decreased intravascular pressures. Some of the commonest causes of pre-renal AKI are summarised in Fig. 17.2. Perfusion of the kidneys at the level of the microvascular beds (glomerular and tubulo-interstitial) is usually maintained through wide variations in pressure and flow through highly efficient auto-regulatory pathways, such as the renin–angiotensin–aldosterone system (RAAS) and

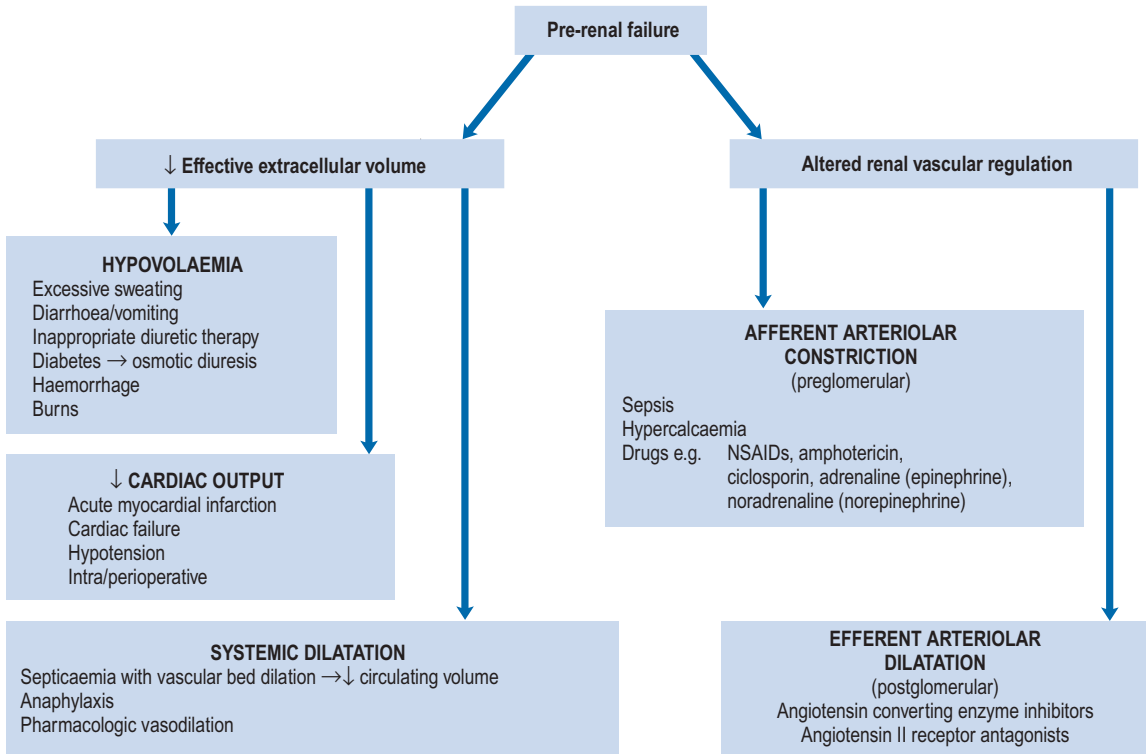


Fig. 17.2 Causes of pre-renal failure.

regulated prostaglandin synthesis. However, when the systolic blood pressure (BP) drops below 80 mmHg, AKI may develop. In individuals with chronic kidney disease (CKD) or in the elderly, this may occur at higher levels of systolic BP. Drugs that inhibit the RAAS, such as angiotension converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), or block the production of prostaglandins, such as non-steroidal anti-inflammatory drugs (NSAIDs), can pre-dispose to the development of pre-renal AKI. These are discussed in more detail below.

Hypovolaemia

This results from any condition that causes intravascular fluid depletion, either directly by haemorrhage or indirectly to compensate for extravascular loss. Examples of this include diarrhoea and vomiting, burns and excessive use of diuretics. Hypotension is a secondary effect of significant hypovolaemia.

Hypotension

In addition to hypovolaemia, hypotension can result from pump (cardiac) failure, of which there are a number of causes, the most common of which is ischaemic heart disease. Another important cause is septic shock, where there is peripheral vasodilatation and low peripheral resistance which leads to profound hypotension despite a high cardiac output.

Intra-renal acute kidney injury

This is caused by a variety of causes (see Tables 17.1 and 17.2), most commonly (in >80% of cases) acute tubular necrosis (ATN). ATN occurs usually as a consequence of a combination of factors, including hypotension, often in the setting of sepsis and nephrotoxic agents including drugs or chemical poisons, or endogenous sources such as myoglobin or haemoglobin.

Acute tubular necrosis

ATN is a diagnosis made by renal biopsy; the findings can include damage to the proximal tubule and the ascending limb of the loop of Henle, interstitial oedema and sparse infiltrating inflammatory cells. Whilst severe and sustained hypoperfusion can lead to ATN, it usually develops when there is a combination of factors including the presence of one or more of a range of nephrotoxins. These may arise exogenously from drugs or chemical poisons, or from endogenous sources such as haemoglobin, myoglobin, crystals (uric acid, phosphate) and toxic products from sepsis or tumours (see Table 17.2). Some endogenous toxins may be released as a direct consequence of drug exposure. For example, myoglobin may be released (rhabdomyolosis) following muscle injury or necrosis, hypoxia, infection or following drug treatment, for example, with fibrates and statins, particularly when both are used in combination. The mechanism of the subsequent damage to renal tissue is not

Table 17.2 Common clinical factors known to cause acute tubular necrosis

Clinical factor	Mechanism
Hypoperfusion	Reduced oxygen/nutrient supply
Radiocontrast media	Medullary ischaemia may result from contrast media induced renal vasoconstriction. The high ionic load of contrast media may produce ischaemia particularly in diabetics and those with myeloma (who produce large quantities of light chain immunoglogulins)
Sepsis	Infection produces endotoxaemia and systemic inflammation in combination with a pre-renal state and nephrotoxins. The immunological response to sepsis involves release of vasoconstrictors and vasodilators (e.g. eicosanoids, nitric oxide) and damage to vascular endothelium with resultant thrombosis
Rhabdomyolysis	Damaged muscles release myoglobin, which can cause ATN through direct nephrotoxicity and by a reduction in blood flow in the outer medulla
Renal transplantation	The procedures and conditions encountered during renal transplantation can induce ischaemic ATN which can be difficult to distinguish from the nephrotoxic effects of immunosuppressive drug therapy used in these circumstances and rejection
Hepatorenal syndrome	Renal vasoconstriction is frequently seen in patients with end-stage liver disease. Progression to ATN is common
Nephrotoxins	
Aminoglycosides	Aminoglycosides are transported into tubular cells where they exert a direct nephrotoxic effect. Current dosage regimens recommend once daily doses, with frequent monitoring of drug levels, to minimise total uptake of aminoglycoside
Amphotericin	Amphotericin appears to cause direct nephrotoxicity by disturbing the permeability of tubular cells. The nephrotoxic effect is dose dependent and minimised by limiting total dose used, rate of infusion and by volume loading. These precautions also apply to newer liposomal formulations

Continued

Table 17.2 Common clinical factors known to cause acute tubular necrosis—cont'd

Clinical factor	Mechanism
Immunosuppressants	Ciclosporin and tacrolimus cause intra-renal vasoconstriction that may result in ischaemic ATN. The mechanism is unclear but enhanced by hypovolaemia and other nephrotoxic drugs
NSAIDs	Vasodilator prostaglandins, mainly E_2, D_2 and I_2 (prostacyclin), produce an increase in blood flow to the glomerulus and medulla. In normal circumstances, they play no part in the maintenance of the renal circulation. However, increased amounts of vasoconstrictor substances arise in a variety of clinical conditions such as volume depletion, congestive cardiac failure or hepatic cirrhosis associated with ascites. Maintenance of renal blood flow then becomes more reliant on the release of vasodilatory prostaglandins. Inhibition of prostaglandin synthesis by NSAIDs may cause unopposed arteriolar vasoconstriction, leading to renal hypoperfusion
Cytotoxic chemotherapy	For example, cisplatin
Anaesthetic agents	Methoxyflurane, enflurane
Chemical poisons/naturally occurring poisons	Insecticides, herbicides, alkaloids from plants and fungi, reptile venoms

understood fully but probably results from a combination of factors including hypoperfusion, haem-catalysed free radical tubular cytotoxicity and haem cast formation and precipitation leading to tubular injury.

The vascular bed and development of acute tubular necrosis. Regional blood flow within the kidney varies, resulting in relatively hypoxic regions such as the outer medulla. This area is also the site of highly metabolically active parts of the nephron. Owing to the relatively poor oxygen supply and high metabolic demands, the outer medulla is at risk of ischaemia, even under normal conditions. The regulation of regional blood flow in the kidney, and therefore the oxygen supply to these areas, relies upon vasomotor mechanisms mediated in part by adenosine. Adenosine appears to exert either vasoconstrictor or vasodilator effects within the kidney depending upon the relative distribution of A_1 and A_2 receptors.

Clearly, any circumstance that interferes with the delicate balance of blood flow and, therefore, oxygen supply within the kidney can result in ATN because of ischaemia and a greater vulnerability to nephrotoxins. The likelihood of ATN is increased by underlying conditions that pre-dispose to ischaemia such as pre-existing CKD of any cause, atheromatous renovascular disease and cholesterol embolisation from upstream atheromatous plaque rupture.

Common causes of acute tubular necrosis. Table 17.2 shows a summary of some of the common factors encountered clinically that may cause ATN.

Immune and inflammatory renal disease

The kidney is vulnerable to a range of immunological processes that can cause AKI. These are divided into glomerular causes (glomerulonephritis) and interstitial causes (interstitial nephritis). Rarely, acute pyelonephritis, which is an infection of renal parenchyma, usually as a consequence of ascending infection, can cause AKI.

Rapidly progressive glomerulonephritis

Glomerulonephritis refers to an inflammatory process within the glomerulus. If that process causes AKI it is called rapidly progressive glomerulonephritis (RPGN). This is an important cause of AKI occurring without a precipitating other illness. Most cases of RPGN are caused by a small vessel vasculitis; this gives a pattern of injury in the glomerulus that is called a focal segmental necrotising glomerulonephritis (FSNGN) with crescent proliferation; crescents are the presence of cells and extra-cellular matrix in Bowman's space. Most cases of FSNGN are caused by anti-neutrophil cytoplasmic antibody-associated small-vessel vasculitis (SVV). Anti-neutrophil cytoplasmic antibodies (ANCA) refer to the presence of circulating antibodies that are targeted against primary neutrophil cytoplasmic antigens (proteins including proteinase 3 and myeloperoxidase).

The two main types of anti-neutrophil cytoplasmic antibody-associated SVV are Wegener's granulomatosis and microscopic polyangiitis. Other important causes of RPGN include Goodpasture's disease, which is caused by antibodies against glomerular basement membrane (anti-GBM antibodies), Systemic lupus erythematosis (SLE) which usually affects young women and is more common with black ethnicity, and secondary vasculitis are triggered by drugs, infection and tumours. There are many drug triggers for secondary vasculitis; the commonest clinical presentation is a cutaneous vasculitis, secondary to immune complex deposition. Kidney involvement can occur and has been reported with a range of drugs.

Interstitial nephritis

Interstitial nephritis is thought to be a nephrotoxin-induced hypersensitivity reaction associated with infiltration of inflammatory cells into the interstitium with secondary involvement of the tubules. The nephrotoxins involved are usually drugs and/or the toxic products of infection. Drugs that have been

most commonly shown to be responsible include NSAIDs, antibiotics (especially penicillins, cephalosporins and quinolones), proton pump inhibitors such as omeprazole, furosemide, allopurinol and azathioprine, although many other drugs have been implicated.

Differentiating pre-renal from renal acute kidney injury

It is sometimes possible to distinguish between cases of pre-renal and renal AKI through examination of biochemical markers (see Table 17.3). In renal AKI, the kidneys are generally unable to retain Na^+ owing to tubular damage. This can be demonstrated by calculating the fractional excretion of sodium (FENa); in practice this is not often done because it lacks sensitivity and specificity and may be difficult to interpret in the elderly who may have pre-existing concentrating defects.

$$\text{FENa} = \text{sodium clearance/creatinine clearance}$$

$$\text{FENa} = \frac{\text{urine sodium} \times \text{serum creatinine}}{\text{serum sodium} \times \text{urine creatinine}}$$

If FENa <1%, this indicates pre-renal AKI with preserved tubular function; if FENa >1% this is indicative of ATN. This relationship is less robust if a patient with renal AKI has glycosuria, pre-existing renal disease, has been treated with diuretics, or has other drug-related alterations in renal haemodynamics, for example, through use of ACE inhibitors or NSAIDs. One potential use of urinary electrolytes is in the patient with liver disease and AKI; where the diagnosis of hepato-renal syndrome is being considered, one of the diagnostic criteria is a urinary sodium <10 mmol/L

Post-renal acute kidney injury

Post-renal AKI results from obstruction of the urinary tract by a variety of mechanisms. Any mechanical obstruction from the renal pelvis to the urethral orifice can cause post-renal AKI; these can be divided into causes within the ureters (e.g. calculi or clots), a problem within the wall of ureter (malignancies, benign strictures) and external compression (e.g. retroperitoneal tumours). It is extremely unusual for drugs to be responsible for post-renal AKI. Practolol-induced retroperitoneal fibrosis resulting in bilateral ureteric obstruction is a rare example.

Table 17.3 Differentiating pre-renal from renal acute kidney injury

Laboratory test	Pre-renal	Renal
Urine osmolality (mOsm/kg)	>500	<400
Urine sodium (mEq/L)	<20	>40
Urine/serum creatinine (µmol/L)	>40	<20
Urine/serum urea (µmol/L)	>8	<3
Fractional excretion of sodium (%)	<1	>2

Clinical manifestations

The signs and symptoms of AKI are often non-specific and the diagnosis can be confounded by coexisting clinical conditions. The patient may exhibit signs and symptoms of volume depletion or overload, depending upon the precipitating conditions, course of the disease and prior treatment.

Acute kidney injury with volume depletion

In those patients with volume depletion, a classic pathophysiological picture is likely to be present, with tachycardia, postural hypotension, reduced skin turgor and cold extremities (see Table 17.4). The most common sign in AKI is oliguria, where urine production falls to less than 0.5 mL/kg/h for several hours. This is below the volume of urine required to effectively excrete products of metabolism to maintain a physiological steady state. Therefore, the serum concentration of those substances normally excreted by the kidney will rise and differentially applies to all molecules up to a molecular weight of around 50 kDa. This includes serum creatinine, which at a molecular weight of 113 Da is normally freely filtered by the kidneys but with loss of kidney function the serum level climbs. Whilst the term uraemia is still in widespread use, it merely describes a surrogate for the overall metabolic disturbances that accompany AKI; these include excess potassium, hydrogen ions (acidosis) and phosphate in blood. Most cases of AKI are first identified by an abnormal blood test, though some patients may have symptoms that are specifically attributable to AKI; these include nausea, vomiting, diarrhoea, gastro-intestinal haemorrhage, muscle cramps and a declining level of consciousness.

Table 17.4 Factors associated with acute kidney injury

	Volume depletion	Volume overload
History	Thirst Excessive fluid loss (vomiting or diarrhoea) Oliguria	Weight increase Orthopnoea/nocturnal dyspnoea
Physical examination	Dry mucosae ↓ Skin elasticity Tachycardia ↓ Blood pressure ↓ Jugular venous pressure	Ankle swelling Oedema Jugular venous distension Pulmonary crackles Pleural effusion

Acute kidney injury with volume overload

In those patients with AKI who have maintained a normal or increased fluid intake as a result of oral or intravenous administration, there may be clinical signs and symptoms of fluid overload (see Table 17.4).

Diagnosis and clinical evaluation

In hospitalised patients, AKI is usually diagnosed incidentally by the detection of increasing serum creatinine and/or a reduction in urine output.

The assessment of renal function is described in detail in Chapter 18. However, unless a patient is at steady state, measurement of serum creatinine does not provide a reliable guide to renal function. For example, serum creatinine levels will usually rise by only 50–100 µmol/L per day following complete loss of renal function in a previously normal patient. These changes in serum creatinine are not sufficiently responsive to serve as a practical indicator of glomerular filtration rate, particularly in AKI in critical care scenarios.

In the hospital situation, when AKI is detected incidentally, the cause(s) of the condition, such as fluid depletion (hypovolaemia), infection or the use of nephrotoxic drugs, are often apparent on close examination of the clinical history. The development of AKI in this setting is more likely to occur in people with pre-existing CKD. People with normal baseline kidney function usually need to sustain at least two separate triggers for the development of AKI; for example, hypovolaemia will rarely cause AKI in this setting, but when hypovolaemia occurs in the presence of nephrotoxic drugs then AKI may occur. In patients with pre-existing CKD, AKI (i.e. acute on chronic renal failure) can occur in patients with one trigger. By definition, the worse the baseline kidney function, the smaller the trigger required for the development of AKI. Irrespective of the presentation of AKI, it is wise to consider the complete differential diagnosis in all people; active exclusion of post-renal AKI and immune and inflammatory AKI should be considered in all cases. In AKI without an obvious precipitating pre-or post-renal cause, there is a greater need to consider these causes. Although the majority of patients have ATN, other causes such as rapidly progressive glomerulonephritis, interstitial nephritis, multiple myeloma or urinary tract obstruction must be screened for and systematically excluded. In addition to supportive care that is generic for all causes of AKI, disease-specific treatment may also be required. The investigation of AKI is outlined in Fig. 17.3.

Various other parameters should be monitored through the course of AKI. Fluid balance charts that are frequently used may be inaccurate and should not be relied upon exclusively. Records of daily weight are more reliable but are dependent on the mobility of the patient.

Monitoring fluid balance in acute kidney disease

Maintaining appropriate fluid balance in AKI is a critical component of the clinical management of the patient. Detailed clinical assessment includes:

1. Measurement of BP which needs to be interpreted in respect of the baseline for the affected patient together with the patient's heart rate.
2. Auscultation of the heart for the presence of 3rd (and 4th) heart sounds; the presence of these indicate cardiac strain associated with fluid overload.
3. Presence of added sounds in the chest, in particular fine inspiratory crackles that are found in some patients with pulmonary oedema.
4. A chest X-ray for the presence of pulmonary oedema.
5. Pulse oximetry to assess arterial oxygen saturation.
6. Whilst the presence of pitting oedema of the legs or sacrum indicates longer term fluid overload, it may be a useful marker of overall endothelial function and the potential for extravascular fluid accumulation.
7. Decreased skin turgor is a sign of fluid loss.

Intravascular monitoring

Central venous pressure (CVP) can be measured following insertion of a central venous catheter, and is a measure of the pressure in the large systemic veins and the right atrium produced by venous return. CVP assesses circulating volume and, therefore, the degree of fluid deficit, and reduces the risk of pulmonary oedema following over-rapid transfusion. CVP should usually be maintained within the normal range of 5–12 cmH_2O.

Most patients with AKI do not require invasive monitoring to the extent described above and recover with supportive care based on careful clinical observations.

Monitoring key parameters in acute kidney disease

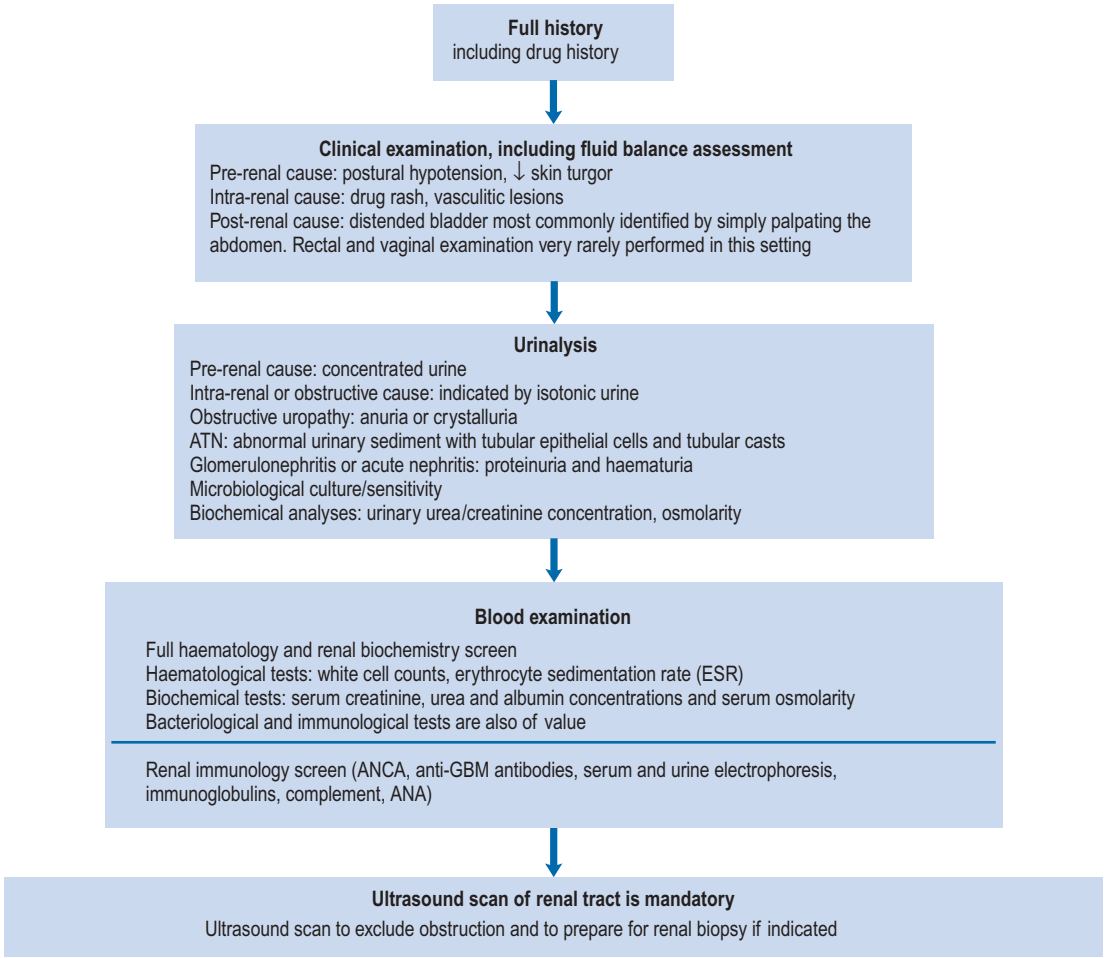
Serum electrolytes including potassium, bicarbonate, calcium, phosphate and acid–base balance should be measured on a daily basis. In patients with severe AKI, acid–base balance may need assessing every few hours as this may direct fluid replacement, respiratory support and dialysis treatment.

Course and prognosis

Pre-renal acute kidney injury

The majority of cases will recover within days of onset following prompt correction of the underlying causes. The urine output improves and waste products of metabolism are cleared by the kidneys. Whilst the kidney function usually stabilises to the pre-event baseline, in some patients long-term kidney function resets to lower than previous values.

ATN may be divided into three phases. The first is the oliguric phase where patients have sustained pre-renal AKI and move from the potential for early reversibility to a situation where uraemia and hyperkalaemia develop and the patient may die unless renal replacement therapy (RRT) with dialysis



ANCA – anti-neutrophil cytoplasmic antibodies
GBM – glomelular basement membrane
ANA – anti nuclear antibody

Fig. 17.3 The investigations of acute kidney injury.

is started. The oliguric phase is usually no longer than 7–14 days but may last for 6 weeks. This is followed by a diuretic phase, which is characterised by a urine output that rises over a few days to several litres per day. This phase lasts for up to 7 days and corresponds to the recommencement of tubular function. The onset of this phase is associated with an improving prognosis unless the patient sustains an intercurrent infection or a vascular event. Finally, the patient enters a recovery phase where tubular cells regenerate slowly over several months, although the glomerular filtration rate often does not return to initial levels. The elderly recover renal function more slowly and less completely.

The mortality rate of AKI varies according to the cause but increases when AKI occurs in patients with multi-organ failure, where mortality rates of up to 70% are seen. Higher mortality rates are seen in patients aged over 60 years.

Death resulting from uraemia and hyperkalaemia are very uncommon. Consequently, the major causes of death associated with AKI are septicaemia and intercurrent acute vascular events such as myocardial infarction and stroke. High circulating levels of uraemic toxins that occur in AKI result in general debility. These, together with the significant number of invasive procedures such as bladder catheterisation and intravascular cannulation which are necessary in the management of AKI, leave such patients prone to infection and septicaemia. Uraemic gastro-intestinal haemorrhage is a recognised consequence of AKI, probably as a result of reduced mucosal cell turnover.

Post-renal acute kidney injury

Prompt identification and relief of the obstruction is important. The prognosis is then dependent on the underlying cause of the obstruction of the renal tract and the baseline to which the kidney function returns after the obstruction has been relieved. If the underlying problem is benign then there may be no long-term adverse consequences. However, if the cause of the obstruction is due to an underlying malignancy then long-term survival is dependent on whether this can be cured.

ACE inhibitors and angiotensin receptor blockers in acute kidney injury

ACE inhibitors and ARBs are not directly nephrotoxic and can be used in most patients with kidney disease. However, profound hypotension can occur if they are initiated in susceptible patients such as those who are receiving high dose diuretics as treatment for fluid overload. This might result in the development of pre-renal AKI. It is, therefore, wise to monitor BP and carefully titrate dosages whilst monitoring renal function in such patients. Nonetheless, it is common to see increases in serum creatinine levels of up to 20% on initiation of an ACE inhibitor or ARB and this is not necessarily a cause for discontinuing therapy with these agents.

ACE inhibitor use is, however, absolutely contraindicated when a patient has bilateral renal artery stenosis, or renal artery stenosis in a patient with a single functioning kidney. If an ACE inhibitor or ARB is initiated under these circumstances then pre-renal AKI may ensue. This may occur since the renin–angiotensin system is stimulated by low renal perfusion resulting from stenotic lesions in the arteries supplying the kidneys, most often at the origin of the renal artery from the abdominal aorta. Angiotensin II is produced which causes renal vasoconstriction, in part, through increased efferent arteriolar tone. This creates a 'back pressure' which paradoxically maintains glomerular filtration pressure in an otherwise poorly perfused kidney. If angiotensin II production is inhibited by an ACE inhibitor, or the effect is blocked by an ARB, then efferent arteriole dilatation will result. Since increased efferent vascular tone maintains filtration in such patients, then the overall result of ACE inhibitor or ARB therapy will be to reduce or shut down filtration at the glomerulus and put the patient at risk of pre-renal AKI (see Fig. 17.4).

Management

The aim of the medical management of a patient with AKI is to prolong life in order to allow recovery of kidney function. Effective management of AKI depends upon a rapid diagnosis. If the underlying acute deterioration in renal function is detected early enough, it is often possible to prevent progression. If the condition is advanced, however, management consists mainly of supportive strategies, with close monitoring and appropriate correction of metabolic, fluid and electrolyte disturbances. Patients with severe AKI usually require renal replacement therapy with dialysis. Specific therapies that promote recovery of ischaemic renal damage remain under investigation. Patients with immune-mediated causes of AKI should be treated with appropriate immunosuppressant regimens to treat the underlying cause of the AKI.

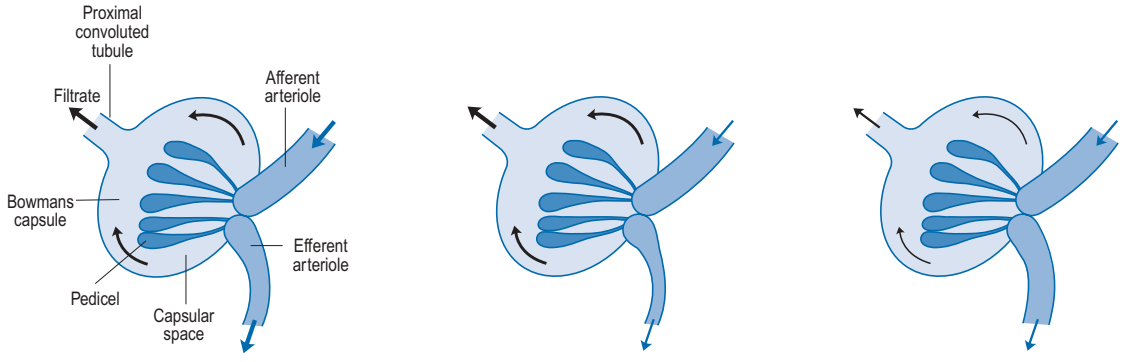
Early preventive and supportive strategies

Identification of patients at risk

Any patient who has concurrent or pre-existing conditions that increase the risk of development and progression of AKI must be identified and this includes those with pre-existing CKD, diabetes, jaundice, myeloma and the elderly. These patients either have baseline impaired renal function or are sensitised to the development of AKI by the co-morbid condition. Meticulous attention to fluid balance, assessment of infection and the use of drugs is crucial to minimise the risk of development of AKI.

Withdrawal and avoidance of nephrotoxic agents

Irrespective of whether the aetiology of the AKI directly involves nephrotoxic drugs, the drug and treatment regimens should be examined so that potential nephrotoxins are



A. Normal glomerulus with efferent arteriolar tone (narrowed outflow of blood) causing a 'back pressure' producing filtration with water and solutes progressing through the capsular space to the proximal convoluted tubule

B. Glomerulus in an untreated patient with renal artery stenosis. There is increased efferent arteriolar tone caused by the vasoconstrictive actions of angiotensin II. The efferent arteriole is narrowed more than normal promoting filtration

C. Glomerulus in a patient with renal artery stenosis but treated with an ACE inhibitor or angiotensin receptor blocker. Blockade of the vasoconstrictive effects of angiotensin II has produced dilation of the efferent arteriole resulting in failure of the back pressure promoting filtration

Fig. 17.4 The actions of ACE inhibition and angiotensin receptor blockade in patients with renal artery stenosis.

withdrawn and avoided in the future in order to avoid exacerbating the condition. Particular care should be taken with ACE inhibitors, NSAIDs, radiological contrast media, and aminoglycosides. The doses should be adjusted of any drugs that are renally excreted or have active metabolites that are excreted renally.

Optimisation of renal perfusion

Initial treatment should include rapid correction of fluid and electrolyte balance to maximise renal perfusion. A central line may be considered to facilitate ease of fluid infusion and monitoring of intravascular volumes. In patients where it is difficult to assess fluid balance by use of clinical examination a urinary catheter may be placed in order that fluid losses may be measured easily. However, with the recent focus on the prevention of catheter-related bacteraemia, central lines are seldom used outside specialist renal and intensive care units.

A diagnosis of acute deterioration of renal function caused by renal underperfusion implies that restoration of renal perfusion would reverse impairment by improving renal blood flow, reducing renal vasoconstriction and flushing nephrotoxins from the kidney. The use of crystalloids in the form of 0.9% sodium chloride is an appropriate choice of intravenous fluid since it replaces both water and sodium ions in a concentration approximately equal to serum. The effect of fluid replacement on urine flow and intravascular pressures should be carefully monitored. However, fluid loading with 1–1.5 L saline at <0.5 L/h is unlikely to cause harm in most patients who do not show signs of fluid overload. There is no evidence that colloids such as gelofusin or albumin provide any additional benefit for volume expansion and renal recovery over the use of 0.9% sodium chloride.

The use of inotropes such as noradrenaline and cardiac doses of dopamine should be restricted to non-renal indications.

Establishing and maintaining an adequate diuresis

Whilst loop diuretics (most commonly furosemide) may facilitate the management of fluid overload and hyperkalaemia in early or established AKI, there is no evidence that these agents are effective for the prevention of, or early recovery from, AKI. It is reasonable to use these agents whilst the urine output is maintained as this provides space for intravenous drugs and parenteral feeding including oral supplements. In experimental settings, loop diuretics decrease renal tubular cell metabolic demands and increase renal blood flow by stimulating the release of renal prostaglandins, a haemodynamic effect inhibited by NSAIDs. However, there is no demonstrable impact on clinical outcomes. Indeed, diuretic therapy should only be initiated in the context of fluid overload. If not, any diuresis might produce a negative fluid balance and precipitate or exacerbate a pre-renal state.

Doses of up to 100 mg/h of furosemide can be given by continuous intravenous infusion. Higher infusion rates may cause transient deafness. The use of continuous infusions of loop diuretics has been shown to produce a more effective diuresis with a lower incidence of side effects than seen with bolus administration. Bolus doses of loop diuretics may induce renal vasoconstriction and be theoretically detrimental to function.

The addition of small oral doses of metolazone may also be considered. Metolazone is a weak thiazide diuretic alone but produces a synergistic action with loop diuretics. In this setting, it should be used with great care as it may initiate a profound diuresis and the patient can rapidly develop intravascular depletion and worsen renal failure

Mannitol. Mannitol has historically been recommended for the treatment of AKI. The rationale for using mannitol in AKI arises from the concept that tubular debris may contribute to oliguria. There is no evidence for mannitol producing benefit in AKI over and above aggressive hydration. Indeed, mannitol can cause volume overload. Consequently, mannitol is now not recommended for patients with AKI.

Dopamine. Historically, dopamine has been recommended at low dose to improve renal blood flow and urine output. Dopamine at low dose acts as a renal vasodilator in normal kidneys, but in renal failure it is a renal vasoconstrictor even at a low dose. This translates into no demonstrable clinical benefit and it should no longer be used. Dopamine has alpha and beta adrenergic effects. Recently, fenoldapam, a pure dopaminergic D_1 agonist has been investigated in small scale clinical trials; the results have shown a trend towards benefit in recovery of renal function from AKI. However, larger trials are needed to identify if fenoldapam has a role in routine clinical practice (Kellum et al., 2008).

Drug therapy and renal auto-regulation

Intra-renal blood flow is controlled by an auto-regulatory mechanism unique to the kidney called tubuloglomerular feedback (TGF). This mechanism produces arteriolar constriction in response to an increased solute load to the distal nephrons. Glomerular filtration rate and kidney workload are thus reduced. It has been proposed that oliguria is an adaptive response to renal ischaemia and therapy designed to improve glomerular filtration rate would increase solute load to the nephrons and might increase kidney workload and worsen AKI. Clearly, reversal of a pre-renal state with fluids is a logical therapeutic aim.

Non-dialysis treatment of established acute kidney injury

Uraemia and intravascular volume overload

In renal failure, the symptoms of uraemia include nausea, vomiting and anorexia, and result principally from accumulation of toxic products of protein metabolism including urea.

Unfortunately, since uraemia causes anorexia, nausea and vomiting, many severely ill patients are unable to tolerate any kind of diet. In these patients and those who are catabolic, the use of enteral or parenteral nutrition should be considered at an early stage.

Intravascular fluid overload must be managed by restricting NaCl intake to about 1–2 g/day if the patient is not hyponatraemic and total fluid intake to less than 1 L/day plus the

volume of urine and/or loss from dialysis. Care should be taken with the so-called 'low salt' products, as these usually contain KCl, which will exacerbate hyperkalaemia.

Hyperkalaemia

This is a particular problem in AKI, not only because urinary excretion is reduced but also because intracellular potassium may be released. Rapid rises in extracellular potassium are to be expected when there is tissue damage, as in burns, crush injuries and sepsis. Acidosis also aggravates hyperkalaemia by provoking potassium leakage from healthy cells. The condition may be life-threatening causing cardiac arrhythmias and, if untreated, can result in asystolic cardiac arrest.

Dietary potassium should be restricted to less than 40 mmol/day and potassium supplements and potassium-sparing diuretics removed from the treatment schedule. Emergency treatment is necessary if the serum potassium level reaches 7.0 mmol/L (normal range 3.5–5.5 mmol/L) or if there are the progressive changes in the electrocardiogram (ECG) associated with hyperkalaemia. These include tall, peaked T waves, reduced P waves with increased QRS complexes or the 'sine wave' appearance that often presages cardiac arrest (see Chapter 18, Fig. 18.10).

Emergency treatment of hyperkalaemia consists of the following:

1. 10–30 mL (2.25–6.75 mmol) of calcium gluconate 10% intravenously over 5–10 min; this improves myocardial stability but has no effect on the serum potassium levels. The protective effect begins in minutes but is short lived (<1 h), although the dose can be repeated.
2. 50 mL of 50% glucose together with 8–12 units of soluble insulin over 10 min. Endogenous insulin, stimulated by a glucose load or administered intravenously, stimulates intracellular potassium uptake, thus removing it from the serum. The effect becomes apparent after 15–30 min, peaks after about 1 h and lasts for 2–3 h and will decrease serum potassium levels by around 1 mmol/L.
3. Nebulised salbutamol has also been used to lower potassium; however, this is not effective for all patients and does not permanently lower potassium. If used it is seen as a temporary emergency measure.

Acidosis

The inability of the kidney to excrete hydrogen ions may result in a metabolic acidosis. This may contribute to hyperkalaemia. It may be treated orally with sodium bicarbonate 1–6 g/day in divided doses (though this is not appropriate for acute metabolic acidosis seen in AKI), or 50–100 mmol of bicarbonate ions (preferably as isotonic sodium bicarbonate 1.4% or 1.26%, 250–500 mL over 15–60 min) intravenously may be used. The administration of bicarbonate in acidotic patients will also tend to reduce serum potassium concentrations. Bicarbonate will cause an increase in intracellular Na^+ through activation of the cell membrane Na^+/H^+ exchanger, which promotes increased activity of Na-K ATPase producing increased intracellular sequestration of K^+.

If calcium gluconate is used to treat hyperkalaemia, care should be taken not to mix it with the sodium bicarbonate (by giving this through the same intravenous access site) as the resulting calcium bicarbonate forms an insoluble precipitate. If elevation of serum sodium or fluid overload precludes the use of sodium bicarbonate, extreme acidosis (serum bicarbonate of less than 10 mmol/L) is best treated by dialysis.

Hypocalcaemia

Calcium malabsorption, probably secondary to disordered vitamin D metabolism, can occur in AKI. Hypocalcaemia usually remains asymptomatic, as tetany of skeletal muscles or convulsions does not normally occur until serum concentrations are as low as 1.6–1.7 mmol/L (normal 2.20–2.55 mmol/L). Should it become necessary, oral calcium supplementation with calcium carbonate is usually adequate, and although vitamin D may be used to treat the hypocalcaemia of AKI, it rarely has to be added. Effervescent calcium tablets should be avoided as they contain a high sodium or potassium load.

Hyperphosphataemia

As phosphate is normally excreted by the kidney, hyperphosphataemia can occur in AKI but rarely requires treatment. Should it become necessary to treat, phosphate-binding agents may be used to retain phosphate ions in the gut. The most commonly used agents are calcium containing such as calcium carbonate or calcium acetate and are given with food. For further information see Chapter18.

Infection

Patients with AKI are prone to infection and septicaemia, which can ultimately cause death. Bladder catheters, central catheters and even peripheral intravenous lines should be used with care to reduce the chance of bacterial invasion. Leucocytosis is sometimes seen in AKI and does not necessarily imply infection. However, pyrexia must be immediately investigated and treated with appropriate antibiotic therapy if accompanied by toxic symptoms such as disorientation or hypotensive episodes. Samples from blood, urine and any other material such as catheter tips should be sent for culture before antibiotics are started. Antibiotic therapy should be broad spectrum until a causative organism is identified.

Other problems

Uraemic gastro-intestinal erosions

These are a recognised consequence of AKI, probably as a result of reduced mucosal cell turnover owing to high circulating levels of uraemic toxins. Proton pump inhibitors are effective and

it is unlikely that any one is more advantageous than another. However, proton pump inhibitors should be used with caution in hospitals where there are significant rates of *Clostridium difficile* diarrhoea, as they may pre-dispose to the development of this organism. H_2 antagonists are an appropriate alternative.

Nutrition

There are two major constraints concerning the nutrition of patients with AKI:

- patients may be anorexic, vomiting and too ill to eat;
- oliguria associated with renal failure limits the volume of enteral or parenteral nutrition that can be given safely.

The introduction of dialysis or haemofiltration allows fluid to be removed easily and, therefore, makes parenteral nutrition possible. Large volumes of fluid may be administered without producing fluid overload. The use of parenteral nutrition is rare but where appropriate factors to be considered include fluid balance, calorie/protein requirements, electrolyte balance/requirements, and vitamin and mineral requirements.

The basic calorie requirements are similar to those in a non-dialysed patient, although the need for protein may occasionally be increased in haemodialysis and haemofiltration because of amino acid loss. In all situations, protein is usually supplied as 12–20 g/day of an essential amino acid formulation, although individual requirements may vary.

Electrolyte-free amino acid solutions should be used in parenteral nutrition formulations for patients with AKI as they allow the addition of electrolytes as appropriate. Potassium and sodium requirements can be calculated on an individual basis depending on serum levels. There is usually no need to try to normalise serum calcium and phosphate levels as they will stabilise with the appropriate therapy, or, if necessary, with haemofiltration or dialysis. Water-soluble vitamins are removed by dialysis and haemofiltration but the standard daily doses normally included in parenteral nutrition fluids more than compensate for this loss. Magnesium and zinc supplementation may be required, not only because tissue repair often increases requirements but also because they may be lost during dialysis or haemofiltration.

It is necessary to monitor the serum urea, creatinine and electrolyte levels daily to make the appropriate alterations in the required nutritional support. The glucose concentration should also be checked daily as patients in renal failure sometimes develop insulin resistance. The plasma pH should be checked initially to determine if addition of amino acid solutions is causing or aggravating metabolic acidosis. It is also valuable to check calcium, phosphate and albumin levels regularly, and when practical, daily weighing gives a useful guide to fluid balance.

Renal replacement therapy

Renal replacement therapy is indicated in a patient with AKI when kidney function is so poor that life is at risk. However, it is desirable to introduce renal replacement therapy early in AKI, as complications and mortality are reduced if the serum urea level is kept below 35 mmol/L. Generally, replacement therapy is urgently indicated in AKI to:

1. remove uraemic toxins when severe symptoms are apparent, for example, impaired consciousness, seizures, pericarditis, rapidly developing peripheral neuropathy
2. remove fluid resistant to diuretics, for example, pulmonary oedema
3. correct electrolyte and acid–base imbalances, for example, hyperkalaemia >6.5 mmol/L or 5.5–6.5 where there are ECG changes, increasing acidosis (pH < 7.1 or serum bicarbonate <10 mmol/L) despite bicarbonate therapy, or where bicarbonate is not tolerated because of fluid overload.

Forms of renal replacement therapy

The common types of renal replacement therapy used in clinical practice are:

- haemodialysis
- haemofiltration
- haemodiafiltration
- peritoneal dialysis

Although the basic principles of these replacement therapies are similar, clearance rates, that is, the extent of solute removal, vary.

In all types of renal replacement therapy, blood is presented to a dialysis solution across some form of semi-permeable membrane that allows free movement of low molecular weight compounds. The processes by which movement of substances occur are:

- *Diffusion.* Diffusion depends upon concentration differences between blood and dialysate and molecule size. Water and low molecular weight solutes (up to a molecular weight of about 5000) move through pores in the semi-permeable membrane to establish equilibrium. Smaller molecules can be cleared from blood more effectively as they move more easily through pores in the membrane.
- *Ultrafiltration*. A pressure gradient (either +ve or −ve) across a semi-permeable membrane will produce a net directional movement of fluid from relative high to low pressure regions. The quantity of fluid dialysed is the ultrafiltration volume.
- *Convection.* Any molecule carried by ultrafiltrate may move passively with the flow by convection. Larger molecules are cleared more effectively by convection.

Haemodialysis

In haemodialysis, the form of access used in AKI is a dialysis line. This is placed in a vein (the jugular, femoral or subclavian), which has an arterial lumen through which the blood is removed from the patient and a venous lumen by which it is returned to the patient after passing through a dialyser. The terms arterial and venous lumen can be misleading as

both lumens are situated in the same vein. They are part of the same line which bifurcates and has two lumens, the longer lumen is the 'arterial' lumen and the shorter the 'venous' lumen. Heparin is added to the blood as it leaves the body to prevent the dialyser clotting. Blood is then actively pumped through the artificial kidney before being returned to the patient (Fig. 17.5). In those patients at high risk of haemorrhage, the amount of heparin used can be reduced or even avoided altogether. The dialyser consists of a cartridge comprising either a bundle of hollow tubes (hollow fibre dialyser) or a series of parallel flat plates (flat-plate dialyser) made of a synthetic semi-permeable membrane. Flat-plate dialysers are now rarely used. Dialysis fluid flows around the membrane countercurrent (opposite) to the flow of blood in order to maximise diffusion gradients. The dialysis solution is essentially a mixture of electrolytes in water with a composition approximating to extracellular fluid into which solutes diffuse. The ionic concentration of the dialysis fluid can be manipulated to control the rate and extent of electrolyte transfer. Calcium and bicarbonate concentrations can also be increased in dialysis fluid to promote diffusion into blood as replacement therapy. By manipulating the hydrostatic pressure of the dialysate and blood circuits, the extent and rate of water removal by ultrafiltration can be controlled.

Haemodialysis can be performed in either intermittent or continuous schedules. The latter regimen is preferable in the critical care situation, providing 24-h control, and minimising swings in blood volume and electrolyte composition that are found using intermittent regimens. The haemodialysis described in this section is indistinguishable from that used as maintenance therapy for many patients with end stage renal failure, the method of access in this group is often via an arterio-venous fistula (see Chapter 18).

The capital cost of haemodialysis is considerable, requires specially trained staff, and is seldom undertaken outside a renal unit. It does, however, treat renal failure rapidly and is, therefore, essential in hypercatabolic renal failure where urea is produced faster than, for example, it could be removed by peritoneal dialysis. Haemodialysis can also be used in patients who have recently undergone abdominal surgery in whom peritoneal dialysis would be ill advised.

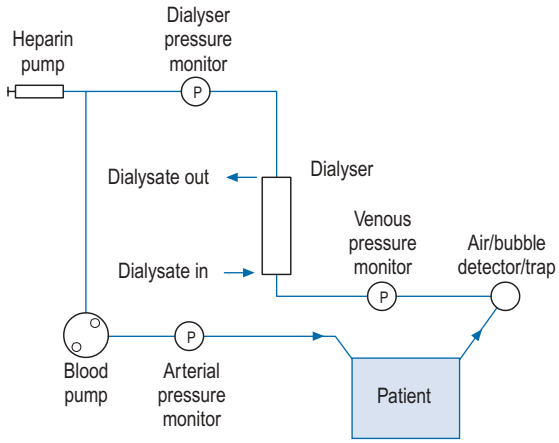


Fig. 17.5 A typical dialysis circuit representing emergency dialysis via a dialysis catheter.

Haemofiltration

Haemofiltration is an alternative technique to dialysis where simplicity of use, fine fluid balance control and low cost have ensured its widespread use in the treatment of AKI.

A similar arrangement to haemodialysis is employed but dialysis fluid is not used. The hydrostatic pressure of the blood drives a filtrate, similar to interstitial fluid, across a high permeability dialyser (passes substances of molecular weight up to 30,000) by ultrafiltration. Solute clearance occurs by convection. Commercially prepared haemofiltration fluid may then be introduced into the filtered blood in quantities sufficient to maintain optimal fluid balance. As with haemodialysis, haemofiltration can be intermittent or continuous. In continuous arterio-venous haemofiltration (CAVH), blood is diverted, usually from the femoral artery, and returned to the femoral vein; this is now very seldom used. In continuous venovenous haemofiltration (CVVH), a dual lumen vascular catheter is inserted into a vein (as described above). Blood is removed from the body via the distal lumen (the one furthest from the right side of the heart) in a process assisted by a blood pump, passed through a haemofilter and returned to the body via the proximal lumen. In slow continuous ultrafiltration (SCU or SCUF), the process is performed so slowly that no fluid substitution is necessary. In addition to avoiding the expense and complexity of haemodialysis, this system enables continuous but gradual removal of fluid, thereby allowing very fine control of fluid balance in addition to electrolyte control and removal of metabolites. This control of fluid balance often facilitates the use of parenteral nutrition. Because of the advantages of haemofiltration over peritoneal dialysis and haemodialysis, continuous haemofiltration is currently the commonest type of renal replacement therapy used in patients in intensive care units.

Haemodiafiltration

Haemodiafiltration is a technique that combines the ability to clear small molecules, as in haemodialysis, with the large molecule clearance of haemofiltration. It is, however, more expensive than traditional haemodialysis, but does offer potential benefits. Whilst some studies suggest that haemodialfiltration may provide a clinical benefit compared to haemofiltration or haemodialysis, this is controversial (Rabindranath et al., 2006). However, enhanced combined control of fluid and solute removal provided by this technique is likely to be increasingly used over the next decade.

Acute peritoneal dialysis

Acute peritoneal dialysis is rarely used now for AKI except in circumstances where haemodialysis is unavailable. A semi-rigid catheter is inserted into the abdominal cavity. Warmed sterile peritoneal dialysis fluid (typically 1–2 L) is

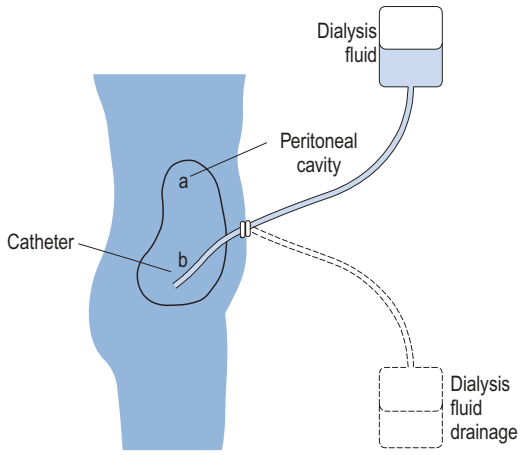


Fig. 17.6 Procedure for peritoneal dialysis.

instilled into the abdomen, left for a period of about 30 min (dwell time) and then drained into a collecting bag (Fig. 17.6). This procedure may be performed manually or by semiautomatic equipment. The process may be repeated up to 20 times a day, depending on the condition of the patient.

Acute peritoneal dialysis is relatively cheap and simple, does not require specially trained staff or the facilities of a renal unit. It does, however, have the disadvantages of being uncomfortable and tiring for the patient. It is associated with a high incidence of peritonitis and permits protein loss, as albumin crosses the peritoneal membrane.

Drug dosage in renal replacement therapy

Whether a drug is significantly removed by dialysis or haemofiltration is an important clinical issue. Drugs that are not removed may well require dose reduction to avoid accumulation and minimise toxic effects. Alternatively, drug removal may be significant and require a dosage supplement to ensure an adequate therapeutic effect is maintained. In general, since haemodialysis, peritoneal dialysis and haemofiltration depend on filtration, the process of drug removal can be considered analoguous to glomerular filtration. Table 17.5 gives an indication of approximate clearances of common renal replacement therapies, which for continuous regimens provide an estimate for the creatinine clearance of the system.

Drug characteristics that favour clearance by the glomerulus are similar to those that favour clearance by dialysis or haemofiltration. These include:

- low molecular weight
- high water solubility
- low protein binding

Table 17.5 Approximate clearances of common renal replacement therapies

Renal replacement therapy	Clearance rate (mL/min)
Intermittent haemodialysis	150–200
Intermittent haemofiltration	100–150
Acute intermittent peritoneal dialysis	10–20
Continuous haemofiltration	5–15

- small volume of distribution
- low metabolic clearance

Unfortunately, a number of other factors inherent in the dialysis process affect clearance; they include:

- duration of dialysis procedure
- rate of blood flow to dialyser
- surface area and porosity of dialyser
- composition and flow rate of dialysate

For peritoneal dialysis other factors come into play and include:

- rate of peritoneal exchange
- concentration gradient between plasma and dialysate

In view of the above, it is usually possible to predict whether a drug will be removed by dialysis, but it is very difficult to quantify the process except by direct measurement, which is rarely practical. Consequently, a definitive, comprehensive guide to drug dosage in dialysis does not exist. However, limited data for specific drugs are available in the literature, while many drug manufacturers have information on the dialysability of their products and some include dosage recommendations in their summaries of product characteristics. The most practical method for treating patients undergoing dialysis is to assemble appropriate dosage guidelines for a range of drugs likely to be used in patients with renal impairment and attempt to restrict use to these.

As drug clearance by haemofiltration is more predictable than in dialysis, it is possible that standardised guidelines on drug elimination may become available. In the interim, a set of individual drug dosage guidelines similar to those described above would be useful in practice.

Factors affecting drug use

How the drug to be used is absorbed, distributed, metabolised and excreted, and whether it is intrinsically nephrotoxic are all factors that must be considered. The pharmacokinetic behaviour of many drugs may be altered in renal failure.

Absorption

Oral absorption in AKI may be reduced by vomiting or diarrhoea, although this is frequently of limited clinical significance.

Metabolism

The main hepatic pathways of drug metabolism appear unaffected in renal impairment. The kidney is also a site of metabolism in the body, but the effect of renal impairment is clinically important in only two situations. The first involves the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (the active form of vitamin D) in the kidney, a process that is impaired in renal failure. Patients in AKI occasionally require vitamin D replacement therapy, and this should be in the form of 1α-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol). The latter is the drug of choice in the presence of concomitant hepatic impairment. The second situation involves the metabolism of insulin. The kidney is the major site of insulin metabolism, and the insulin requirements of diabetic patients in AKI are often reduced.

Distribution

Changes in drug distribution may be altered by fluctuations in the degree of hydration or by alterations in tissue or serum protein binding. The presence of oedema or ascites increases the volume of distribution while dehydration reduces it. In practice, these changes will only be significant if the volume of distribution of the drug is small, that is, less than 50 L. Serum protein binding may be reduced owing to either protein loss or alteration in binding caused by uraemia. For certain highly bound drugs the net result of reduced protein binding is an increase in free drug, and care is, therefore, required when interpreting serum concentrations. Most analyses measure the total serum concentration, that is, free plus bound drug. A drug level may, therefore, fall within the accepted concentration range but still result in toxicity because of the increased proportion of free drug. However, this is usually only a temporary effect. Since the unbound drug is now available for elimination, its concentration will eventually return to the original value, albeit with a lower total bound and unbound level. The total drug concentration may, therefore, fall below the therapeutic range while therapeutic effectiveness is maintained. It must be noted that the time required for the new equilibrium to be established is about four or five elimination half-lives of the drug, and this may be altered itself in renal failure. Some drugs that show reduced serum protein binding include diazepam, morphine, phenytoin, levothyroxine, theophylline and warfarin. Tissue binding may also be affected; for example, the displacement of digoxin from skeletal muscle binding sites by metabolic waste products that accumulate in renal failure result in a significant reduction in digoxin's volume of distribution.

Excretion

Alteration in renal clearance of drugs in renal impairment is the most important parameter to consider when considering dosage. Generally, a fall in renal drug clearance indicates a decline in the number of functioning nephrons. The glomerular filtration rate can be used as an estimate of the number of functioning nephrons. Thus, a 50% reduction in the glomerular filtration rate will suggest a 50% decline in renal clearance.

Renal impairment, therefore, often necessitates drug dosage adjustments. Loading doses of renally excreted drugs are often necessary in renal failure because of the prolonged elimination half-life which leads to an increased time to reach steady state. The equation for a loading dose is the same in renal disease as in normal patients, thus:

$$\text{loading dose (mg)} = \text{target concentration (mg/L)} \times \text{volume of distribution (L)}$$

The volume of distribution may be altered but generally remains unchanged.

It is possible to derive other formulae for dosage adjustment in renal impairment. One of the most useful is:

$$DR_{rf} = DR_n \times [(1 - F_{eu}) + (F_{eu} \times RF)]$$

where DR_{rf} is the dosing rate in renal failure, DR_n is the normal dosing rate, RF is the extent of renal impairment = patient's creatinine clearance (mL/min)/ideal creatinine clearance (120 mL/min) and F_{eu} is the fraction of drug normally excreted unchanged in the urine. For example, when RF = 0.2 and F_{eu} = 0.5, 60% of the normal dosing rate should be given.

An alteration in dosing rate can be achieved by either altering the dose itself or the dosage interval, or a combination of both as appropriate. Unfortunately, it is not always possible to obtain the fraction of drug excreted unchanged in the urine. In practice, it is simpler to use the guidelines for prescribing in renal impairment found in the British National Formulary. These are adequate for most cases, although the specialist may need to refer to other texts.

Nephrotoxicity

The list of potentially nephrotoxic drugs is long. Although the commonest serious forms of renal damage are interstitial nephritis and glomerulonephritis, the majority of drugs only cause damage by hypersensitivity reactions and are safe in many patients. Some drugs, however, are directly nephrotoxic, and their effects on the kidney are more predictable. Such drugs include aminoglycosides, amphotericin, colistin, the polymixins and ciclosporin. The use of any drug with recognised nephrotoxic potential should be avoided where possible. This is particularly true in patients with pre-existing renal impairement or renal failure. Figure 17.7 summarises the most important and common adverse effects of drugs on renal function, indicating the likely regions of the nephron in which damage occurs. Additional information on adverse effects can be found in Hems and Currie (2005).

Inevitably, occasions will arise when the use of potentially nephrotoxic drugs becomes necessary, and on these occasions constant monitoring of renal function is essential. In conclusion, when selecting a drug for a patient with renal failure, an agent should be chosen that approaches the ideal characteristics listed in Box 17.1.

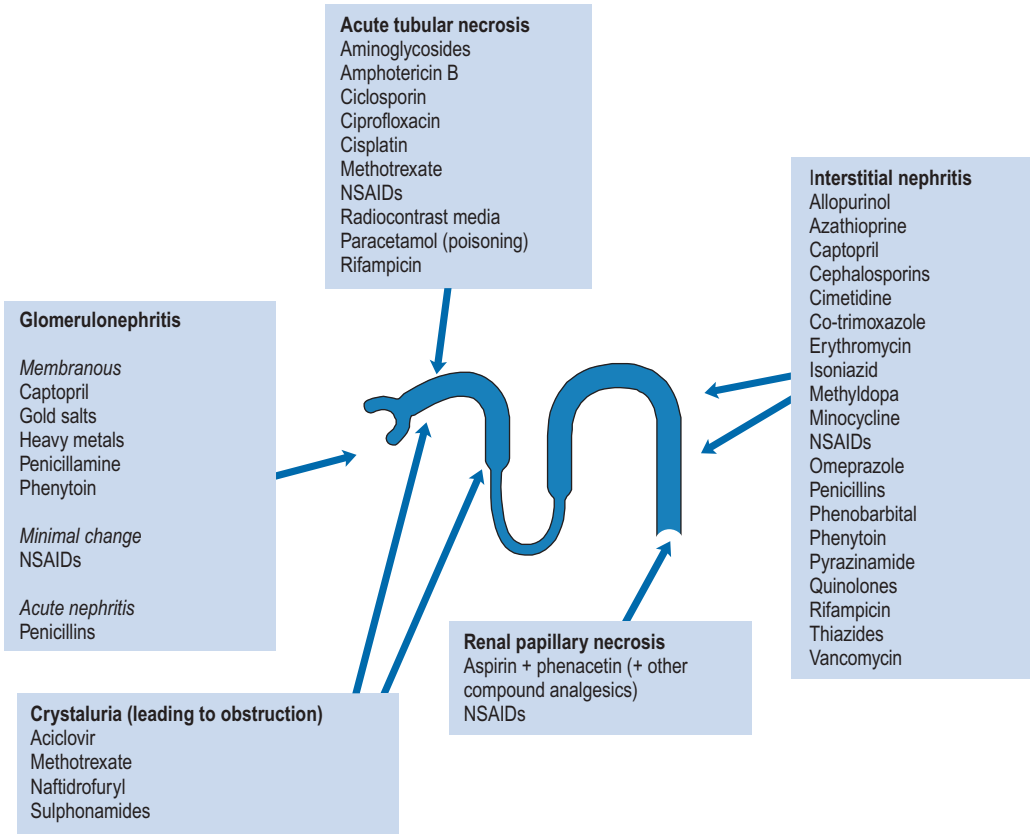


Fig. 17.7 Common adverse effects of drugs on the kidney. The likely sites of damage to the nephron (stylised) are indicated.

Box 17.1 Characteristics of the ideal drug for use in a patient with renal failure

- No active metabolites
- Disposition unaffected by fluid balance changes
- Disposition unaffected by protein binding changes
- Response unaffected by altered tissue sensitivity
- Wide therapeutic margin
- Not nephrotoxic

Case studies

Case 17.1

Mrs J a 60-year-old widow, had long-standing hypertension that was unsatisfactorily controlled on a variety of agents. Her drug therapy included furosemide 40 mg once a day, amlodipine 10 mg daily and a salt restricted diet. Following a routine review of her therapy, ramipril 2.5 mg once daily was added to her treatment regimen in an attempt to improve blood pressure control.

Mrs J was recently diagnosed with gastroenteritis. A week after her diagnosis she presented to her local hospital accident and emergency unit, with ongoing diarrhoea. Her BP was found to be 100/60 mmHg and serum biochemistry revealed creatinine levels of 225 µmol/L (50–120 µmol/L, Na^+ 125 mmol/L (135–145 mmol/l) and K^+ 5.2 mmol/L (3.5–5.0 mmol/L).

Questions

1. What was the likely cause and underlying mechanism to this patients's problem?
2. What treatment should be given?

Answers

1. ACE inhibitors reduce angiotensin II production, thus, attenuate angiotensin II mediated vasoconstriction of the efferent arterioles that contributes to the high-pressure gradient across the glomerulus necessary for filtration. It is not usually a problem in the majority of individuals; however, in patients with pre-existing compromised renal blood flow, such as renal artery stenoses, the kidney relies more heavily on angiotensin-mediated vasoconstriction of the postglomerular arterioles to maintain renal function. Hypovolaemia caused, for example, by diuretic use and a diarrhoeal illness would tend to exacerbate this problem. Moreover, it is likely that sodium depletion would render the kidney even more dependent upon vasoconstriction of efferent arterioles through activation of the tubuloglomerular feedback system, further sensitising the kidney to the effects of ACE inhibitors.

   Mrs J might well have been suffering from incipient renal failure, but remained asymptomatic until her renal reserve diminished.
2. The inappropriate use of an ACE inhibitor should be stopped, as should the diuretic temporarily. Mrs J should be rehydrated using sodium chloride 0.9% and kidney function markers monitored in the hope that recovery will occur.
3. Investigations should be arranged to determine whether Mrs J has renal artery stenosis as a cause of her AKI after initiation of the ACE inhibitor (see Chapter 18).

Case 17.2

Mr B a known intermittent heroin and cocaine abuser, was discovered comatose in his room early in the morning. He was admitted to hospital as an emergency. An indirect history from an acquaintance indicated that Mr B had been drinking very heavily prior to the incident (probably more than a bottle of whisky in a 24-h period) and had smoked both heroin and cocaine of unknown source and purity.

On examination he was found to be dehydrated and serum biochemistry revealed the following:

		Reference range
Sodium	147 mmol/L	(135–145)
Potassium	6.1 mmol/L	(3.5–5.0)
Calcium	1.72 mmol/L	(2.20–2.55)
Phosphate	2.0 mmol/L	(0.9–1.5)
Creatinine	485 µmol/L	(50–120)
Creatinine kinase	120,000 IU/L	(<200)

Urine dipstick reacted positive for blood with no signs of red blood cells on microscopy. The urine was faintly reddish-brown in colour.

Question

What is likely to have occurred and how should it be treated?

Answer

Cocaine, heroin or alcohol abuse sometimes cause muscle damage resulting in rhabdomyolysis. The mechanism is unclear, but includes vasoconstriction, an increase in muscle activity, possibly because of seizures, self-injury, adulterants in the drug (e.g. arsenic, strychnine, amphetamine, phencyclidine, quinine) or compression (associated with long periods of inactivity). ATN may ensue from a direct nephrotoxic effect of the myoglobin released from damaged muscle cells, microprecipitation of myoglobin in renal tubules (as casts) or a reduction in medullary blood flow. The presence of myoglobin is suggested by the urine dipstick test, which reacts not only to red cells but also to free haemoglobin and myoglobin. Extremely high levels of myoglobinuria may result in urine the colour of Coca-Cola. High serum creatinine kinase levels are indicative of rhabdomyolysis together with the presence of free myoglobin in serum and urine. Serum levels of potassium and phosphate are elevated partly by the effects of incipient renal failure but also through tissue breakdown and intracellular release. Creatinine levels are often higher than expected because of muscle damage.

Treatment should involve fluid replacement with normal saline to reverse dehydration. Furosemide and other loop diuretics should be avoided as these decrease intra-tubular pH which may be a co-factor for cast precipitation. Indeed, in cases where urine pH is less than 6, administration of intravenous isotonic sodium bicarbonate may be of use. The patient's ECG should be monitored, because of the risks involved with rapid elevation in serum potassium. Timely, appropriate corrective therapy must be instigated where necessary. In 50–70% of cases with rhabdomyolysis, dialysis is required to support recovery.

Case 17.3

Mr D is a patient who has been admitted to an intensive care unit with AKI, which developed following a routine cholecystectomy. His electrolyte picture shows the following:

		Reference range
Sodium	138 mmol/L	(135–145)
Potassium	7.2 mmol/L	(3.5–5.0)
Bicarbonate	19 mmol/L	(22–31)
Urea	32.1 mmol/L	(3.0–6.5)
Creatinine	572 µmol/L	(50–120)
pH	7.28	(7.36–7.44)

The patient was connected to an ECG monitor and the resultant trace indicated absent P waves and a broad QRS complex.

Question

Explain the biochemistry and ECG abnormalities and indicate what therapeutic measures must be implemented.

Answer

Hyperkalaemia is one of the principal problems encountered in patients with renal failure. The increased levels of potassium arise from failure of the excretory pathway and also from intracellular release of potassium. Attention should also be paid to pharmacological or pharmaceutical processes that might lead to potassium elevation (e.g. inappropriate potassium supplements, ACE inhibitors, etc.). The acidosis noted in this patient, which is common in AKI, also aggravates hyperkalaemia by promoting leakage of potassium from cells. A serum potassium level greater than 7.0 mmol/L indicates that emergency treatment is required as the patient risks life-threatening ventricular arrhythmias and asystolic cardiac arrest. If ECG changes are present, as in this case, emergency treatment should be initiated when serum potassium rises above 6.5 mmol/L.

The emergency treatment should include:

1. Stabilisation of the myocardium by intravenous administration of 10–30 mL calcium gluconate 10% over 5–10 min. The effect is temporary but the dose can be repeated.
2. Intravenous administration of 10–20 units of soluble insulin with 50 mL of 50% glucose to stimulate cellular potassium uptake. The dose may be repeated. The blood glucose should be monitored for at least 6 h to avoid hypoglycaemia.
3. Acidosis may be corrected with an intravenous dose of sodium bicarbonate, preferably as an isotonic solution. Correction of acidosis stimulates cellular potassium re-uptake.
4. Intravenous salbutamol 0.5 mg in 100 mL 5% dextrose administered over 15 min has been used to stimulate the cellular Na-K ATPase pump and thus drive potassium into cells. This may cause disturbing muscle tremors at the doses required to reduce serum potassium levels.

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18 Chronic kidney disease and end-stage renal disease

J. Marriott, P. Cockwell and S. Stringer

Key points

- The prevalence of chronic kidney disease (CKD) increases with age and is greater in females and some ethnic populations.
- CKD is classified according to severity from 1 to 5, where 5 is the most advanced and 1 the least.
- CKD 1–3 is common and may not cause symptoms. It may progress to end-stage renal disease but frequently remains stable for many years.
- CKD is an important risk factor for cardiovascular disease.
- As CKD becomes more advanced (stages 4 and 5), virtually all body systems are adversely affected.
- Clinical signs and symptoms of severe CKD include oedema, anaemia, hypertension, bone pain, nocturia, neurological changes and disordered muscle function.
- The aims of treatment are to reverse or arrest the process responsible for CKD, relieve symptoms and reduce cardiovascular morbidity and mortality.
- To prevent further renal damage, adequate control of blood pressure and reduction of proteinuria are essential.
- Renal anaemia is common when the glomerular filtration rate (GFR) falls below 30 mL/min but can be corrected by erythropoietin in 90–95% of cases.
- End-stage renal disease is the point at which life can only be sustained by dialysis or transplantation. This may occur soon after presentation or after several years.
- The need for dialysis therapy is increasing at about 5% per annum with attendant resource implications.
- There are two principal types of dialysis: haemodialysis and peritoneal dialysis. In both, waste products and metabolites are transferred from the patient's blood across a semi-permeable membrane to a dialysis solution.
- Renal transplantation remains the treatment of choice for end-stage renal disease. However, up to 60% of patients on dialysis programmes are not fit enough to be put on the transplant list.

Chronic kidney disease (CKD) is defined by a reduction in the glomerular filtration rate (GFR) and/or urinary abnormalities or structural abnormalities of the renal tract. The severity of CKD is classified from 1 to 5 depending upon the level of GFR (Table 18.1). It is a common condition affecting up to 10% of the population in Western societies and is more common in some ethnic minority populations and in females. The incidence increases exponentially with age such that some degree of CKD is almost inevitable in persons over 80 years of age. Social deprivation is also associated with a higher prevalence of CKD. The scale of CKD and the consequences for the health service has been appreciated only in the last few years.

Estimates for the incidence of the various grades of CKD are shown in Table 18.1 and have been derived from large American studies, although data suggests the rates in the UK are similar (UK Renal Registry, 2008). In the past, patients with CKD were often unrecognised owing to difficulties in measuring or estimating the GFR and their health needs were largely unmet. The recent development of simple methods to estimate GFR has revealed a huge population of patients with significant kidney disease. This will pose a considerable challenge to health services in the future. National guidance on the management of CKD has been published (NICE, 2008) and includes management in primary and secondary care.

CKD differs from acute kidney injury (AKI) by virtue of chronicity and a different spectrum of causes. However, AKI and CKD are not mutually exclusive; patients with AKI may not recover renal function to their baseline and may be left with residual CKD. In addition, patients with CKD may experience episodes of AKI sometimes causing reversible step-wise declines in renal function.

Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) has a critical role in the progression of CKD and an awareness of this system is important for understanding the pathophysiology of CKD and the targets for therapeutic intervention. Most of the renal effects of this system are through regulating intraglomerular pressures and salt and water balance. Renin is an enzyme which is formed and stored in the juxtaglomerular apparatus and released in response to decreased afferent intra-arterial pressures, decreased glomerular ultrafiltrate sodium levels and sympathetic nervous system activation. In patients with CKD, intra-renal pressures are often low and sympathetic overactivity is common; these factors lead to increased renin secretion. This can occur with normal or elevated systemic blood pressure.

Table 18.1 Classification of chronic kidney disease

Stage of CKD	Glomerular filtration rate	Description	Prevalence in the UK (% of population)
1	≥90 mL/min + proteinuria/haematuria or structural damage	Kidney damage with normal or increased GFR but other evidence of kidney damage	3.3
2	60–89 mL/min + proteinuria/haematuria or structural damage	Slight decrease in GFR with other evidence of kidney disease	3.0
3a 3b	45–59 mL/min 30–44 mL/min	Moderate reduction in GFR With or without evidence of other kidney disease	4.3
4	13–29 mL/min	Severe reduction in GFR	0.2
5	<15 mL/min	Kidney failure, use suffix (D) if dialysis	0.1

GFR, glomerular filtration rate.
Use suffix (P) to denote proteinuria, suffix (D) to denote dialysis and suffix (T) to denote transplantation. For example, a patient with CKD 3a and proteinuria would be described as CKD 3A p. A patient with CKD 5 on dialysis would be CKD5 d

Renin promotes cleavage of the protein angiotensinogen, which is produced by the liver, to produce angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has two major physiological effects. First, it acts on the zona glomerulosa of the adrenal cortex to promote production of the mineralocorticoid hormone aldosterone, with resultant increased distal tubular salt and water reabsorption. Furthermore, it promotes antidiuretic hormone (ADH) release, which increases proximal tubular sodium reabsorption and promotes thirst. In combination, these lead to salt and fluid retention, high intravascular volumes, hypertension and oedema. Second, it is a direct vasoconstrictor and promotes systemic and (preferential) renal hypertension. The renal effects are predominantly on the efferent glomerular arteriole. Vasoconstriction at this site is mediated by a high density of angiotensin II receptors. When these receptors are ligated by angiotensin II, there is increased intra-glomerular pressures. Whilst this leads to an overall increase in GFR in the short-term, over a longer period glomerular hypertension promotes accelerated glomerular scarring and worsening CKD. In addition to the vascular and endocrine effects of the RAAS, it is now recognised that there is a local immune modulatory role for this system. Both resident (e.g. tubular epithelial) cells and inflammatory (monocytes and macrophages) cells synthesise components of the RAAS and are themselves targeted by the system. For example, monocytes and macrophages express the angiotensin II receptor and activation through this receptor leads to an enhanced inflammatory and fibrotic phenotype of the cell. This raises the intriguing concept that some of the effects of blocking the RAAS are due to direct anti-inflammatory and anti-fibrotic effects. Figure 18.1 shows this pathway and identifies the points at which pharmacological interventions targeted for a biological effect translates into clinical outcomes.

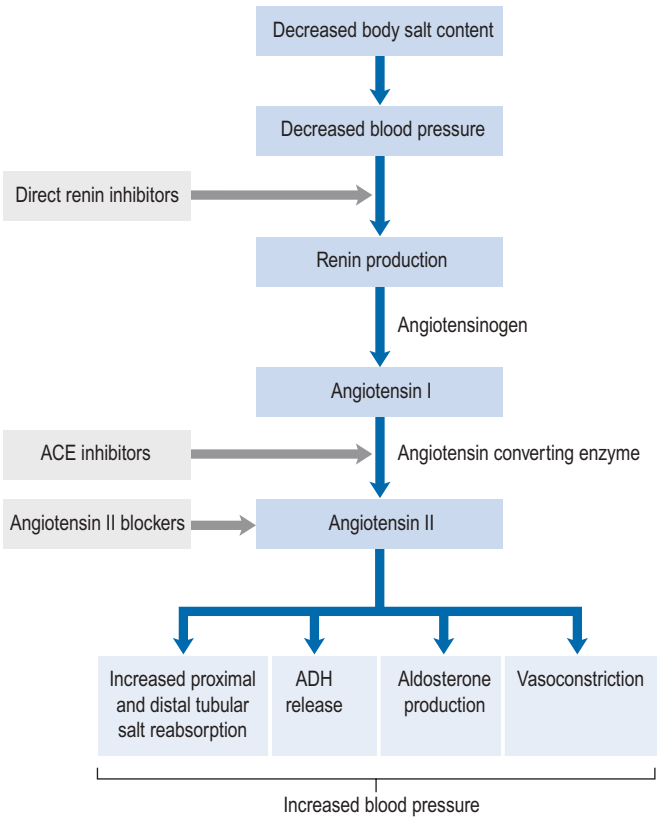

Fig. 18.1 The renin–angiotensin–aldosterone system and targets for pharmaceutical intervention.

Measurement of renal function

The scale of CKD has only been recognised in recent years because detection is dependent upon an accurate estimation of the GFR. The GFR is defined as the volume of filtrate

produced by the glomeruli of both kidneys each minute and is a reliable indicator of renal function.

It is laborious and expensive to measure GFR by gold standard tests such as inulin or radiolabelled isotope clearance. These tests are only used when extremely accurate assessment of kidney function is required. An example of this is measurement of kidney function in a potential living kidney donor where an individual is proposing to donate a kidney to a family member or close friend.

As a consequence, a number of equations have been validated for use in the routine clinical setting. These equations provide an estimate of glomerular filtration rate (eGFR) based on the combination of serum or plasma creatinine and a number of variables which add precision to the estimation of kidney function. The commonest eGFR equation used in clinical practice is the four-variable MDRD (Modification of Diet in Renal Disease Study) equation. The biochemical variable that provides the basis of the MDRD and most other GFR equations is serum creatinine.

Serum creatinine

While serum creatinine concentration is related to renal function, it is also dependent upon the rate of production of creatinine by the patient. Creatinine is a by-product of normal muscle metabolism and is formed at a rate proportional to muscle mass (20 g muscle equates to approximately 1 mg creatinine production) and therefore is related to age, sex and ethnicity.

Creatinine is freely filtered by the glomerulus, so when muscle mass is stable any change in serum creatinine levels reflects a change in its renal clearance. Consequently, measurement of serum creatinine can be utilised to give an estimate of the kidney function. It is important to note, however, that creatinine also undergoes significant tubular secretion (~10–20%). This becomes important in advanced CKD (stages 4 and 5) and limits the value of measuring serum creatinine to determine renal function in advanced CKD.

MDRD glomerular filtration rate equation

Eight eGFR equations were validated for the MDRD study (Levey et al., 1999). These used demographic and serum variables (including serum creatinine level, age, gender, non-black ethnicity, higher serum urea levels, and lower serum albumin levels) in a series of equations. The four-variable equation (also known as the abbreviated (a)MDRD equation) has been adopted into clinical practice and incorporates age, creatinine, gender and ethnicity (Fig. 18.2).

The MDRD equation is more accurate than serum creatinine alone as an estimator of kidney function; however, it has not been validated in the elderly, those with creatinine levels within the normal range or transplant recipients. The CKD classification system is based on the aMDRD eGFR.

Other estimates of kidney function

Creatinine clearance

This is similar to the GFR as nearly all the filtered creatinine appears in the urine. It is a measurement of the volume of blood that is cleared of creatinine with time. Measurements of creatinine clearance (Cl_{Cr}) require accurate collection of 24 h urine samples with a serum creatinine sample midway through this period. This is time-consuming, inconvenient and prone to inaccuracy and as such is now rarely used in clinical practice. Figure 18.3 shows the equation for measuring creatinine clearance.

Cockroft–Gault equation

The Cockroft–Gault equation uses weight, sex and age to estimate creatinine clearance and was derived using average population data (Cockroft and Gault, 1976). The equation is shown in Fig. 18.4.

Estimates of glomerular filtration rate in paediatric patients

Estimates of GFRs in paediatric patients can be made using the Schwartz formula (Schwartz, 1985) or the Counahan–Barratt method (Counahan et al., 1976) which both rely upon inclusion of the height of the child in estimating creatinine clearance, since height correlates with muscle mass.

Urea

Urea is also used in the assessment of renal function despite a variable production rate and diurnal fluctuation in response to the protein content of the diet. Levels of urea

$$Cl_{Cr} = \frac{(U \times V)}{S}$$

where U is the urine creatinine concentration (μmol/L), V is the urine flow rate (mL/min) and S is the serum creatinine concentration (μmol/L)

Fig. 18.3 Creatinine clearance calculation.

$$Cl_{Cr} = \frac{F\,(140 - \text{age (years)}) \times \text{weight (kg)}}{\text{Serum creatinine (μmol/L)}}$$

where F = 1.04 (females) or 1.23 (males)

Fig. 18.4 The Cockroft–Gault formula.

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 186 \times [\text{serum creatinine (μmol/L)}/88.4]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if } \textbf{female}] \times [1.212 \text{ if } \textbf{African-American}]$$

Fig. 18.2 Four-variable MDRD equation used to calculate eGFR.

may also be elevated by dehydration or an increase in protein catabolism such as that accompanying gastro-intestinal haemorrhage, severe infection, trauma (including surgery) and high-dose steroid therapy. Serum urea levels are, therefore, an unreliable measure of renal function, but can be used as an indicator of the patient's general condition and state of hydration. A rapid elevation of serum urea, before any rise in corresponding creatinine levels, is often a sign of an impending deterioration in renal function or a marker for pre-renal failure associated with intravascular volume depletion.

Significance of CKD

CKD is significant as it indicates the possibility of progression to end-stage renal disease, and a strong association with accelerated cardiovascular disease, similar in magnitude to that observed in diabetics. The cardiovascular risk increases with the severity of CKD but is detectable at all levels. Thus, it is important to pay particular attention to traditional cardiovascular risk factors such as smoking, cholesterol and blood pressure in patients with CKD. However, it is known from previous studies that these risk factors only contribute around 50% of the total cardiovascular disease risk and recent interest has focused on the identification of novel risk factors to explain the remainder of the risk.

It is important to make a distinction between cardiovascular disease related to macrovascular atherosclerosis and that related to microvascular changes, often found in individuals with CKD. The cardiovascular disease found in CKD is more likely to be related to small vessel disease initiated by endothelial dysfunction rather than atherosclerotic disease. In addition, patients with CKD often have associated left ventricular hypertrophy which may be related to chronic volume overload and uraemia.

Progression to more advanced stages of CKD may occur, particularly if the blood pressure is inadequately controlled and there is significant proteinuria, but this is by no means the rule and many patients with CKD remain stable for years or even decades. These patients need to be followed up with regular blood and urine tests to detect progression, if it occurs. Low risk patients, that is, those with unchanging GFR over time, with controlled blood pressure and no proteinuria may not require long-term follow up by a kidney specialist and surveillance can be carried out satisfactorily in primary care.

Patients with CKD 1–3 (Table 18.1) are frequently asymptomatic. The reduction of GFR is insufficient to cause uraemic symptoms and any minor abnormalities in the urine such as proteinuria or haematuria are usually not noticed by patients. There is a frequent association with high blood pressure which may be the cause or a consequence of renal damage. Recognition of these patients is important as it allows early modification of traditional cardiovascular risk factors. These patients should be investigated to determine if there is a treatable cause for their CKD and followed up to identify those individuals with progressive disease.

Patients with CKD stages 4 and 5 (Table 18.1) should usually be followed up in a nephrology clinic because they will require specialist management of the complications of CKD such as anaemia and bone disease, whilst many will also be undergoing preparation for renal replacement therapy.

Causes of CKD

The reduction in renal function observed in CKD results from damage to the infrastructure of the kidney in discrete areas rather than throughout the kidney. The nephron is the functional unit of the kidney and while the mechanism of damage depends on the underlying cause of renal disease, as nephrons become damaged and fail, remaining nephrons compensate for loss of function by hyperfiltration secondary to raised intra-glomerular pressure. This causes 'bystander' damage with secondary nephron loss. This vicious cycle is illustrated in Fig. 18.5. The patient remains well until so many nephrons are lost that the GFR can no longer be maintained despite activation of compensatory mechanisms. As a consequence there is a progressive decline in kidney function.

CKD arises from a variety of causes (Table 18.2), although by the time a patient has established CKD it may not be possible to identify the exact cause. However, attempting to establish the cause is useful in the identification and elimination of reversible factors, to plan for likely outcomes and treatment needs, and for appropriate counselling when a genetic basis is established. The causes of CKD listed in Table 18.2 are ordered according to prevalence. It is important to note the prevalence of these factors is different in CKD and end stage renal disease. In end stage renal disease, diseases such as adult polycystic kidney disease (APKD) are overrepresented and ischaemic/hypertensive nephropathy underrepresented. The reasons for this are that individuals with APKD are likely to survive to reach end stage renal disease while those with diabetes or ischaemic renal damage may succumb to cardiovascular disease before end stage renal disease is reached.

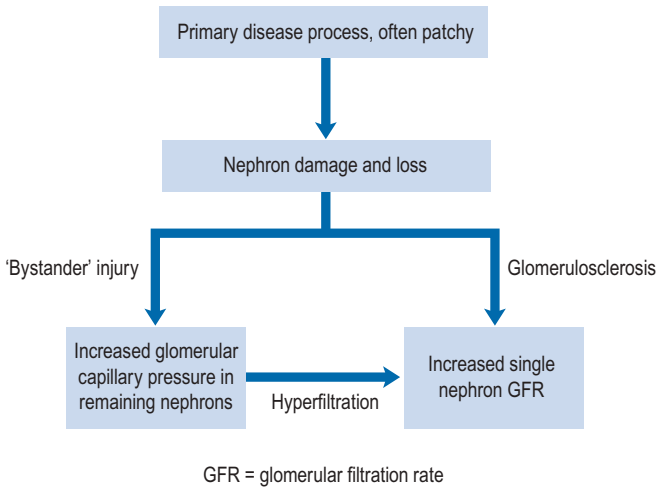

Fig. 18.5 Mechanism of progressive renal damage.

Table 18.2 Primary diagnosis in renal replacement therapy patients by age and gender (Renal Registry, 2008)

Primary diagnosis	% all patients	Inter-centre range (%)	% age <65	% age >65	% male:female ratio
Aetiology uncertain/ glomerulonephritis (not biopsy proven)	21.6	2.1–84.3	19.2	26.6	1.6
Glomerulonephritis (biopsy proven)	15.3	2.3–22.4	17.8	10.0	2.2
Pyelonephritis	11.9	3.2–19.4	13.6	8.3	1.1
Diabetes	13.2	2.8–26.0	12.3	15.1	1.6
Polycystic kidney	9.2	2.0–15.8	9.6	8.3	1.1
Hypertension	5.4	1.0–16.0	4.6	6.9	2.4
Renal vascular disease	3.5	0.3–16.1	1.1	8.2	2.0
Other	14.5	1.9–36.1	16.0	11.3	1.3
Not sent	5.5	0.1–46.2	5.7	5.2	1.5

Ischaemic/hypertensive renal disease

Ischaemic nephropathy has traditionally been referred to under perfusion of the kidneys caused by renal artery stenosis. This explanation has fallen from favour recently and this term is now taken to mean impairment of renal function beyond occlusion of the main renal arteries. Hypertension results in atherosclerosis which can cause occlusive renovascular disease and small vessel damage. In patients with significant large vessel occlusive disease arteriolar nephrosclerosis, interstial fibrosis and glomerular collapse may be present (Lerman and Textor, 2001). These diagnoses account for around 30% of CKD and a smaller proportion of end stage renal disease. The effective management of hypertension is crucial to reduce renal damage.

Metabolic diseases

Diabetes mellitus is the most common metabolic disease that leads to CKD, whilst the predominant lesion is glomerular and referred to as diabetic nephropathy. Diabetes accounts for around 13% of CKD (see Table 18.2) and is associated with faster renal deterioration than other pathologies: these patients are at very significant cardiovascular risk by virtue of both CKD and diabetes. Both type 1 and 2 diabetes can result in diabetic nephrophy, patients with type 1 diabetes usually present with renal complications at a younger age and may benefit from combined kidney and pancreas transplantation. Patients with diabetes may present with no proteinuria, micro albuminuria or overt proteinuria, though as the level of proteinuria increases the GFR usually declines and in many patients this represents an inexorable decline towards end stage renal disease.

Chronic glomerulonephritis

All types of chronic glomerulonephritis (GN) combined cause about 15% of cases of advanced CKD. The commonest cause of glomerulonephritis is IgA nephropathy which is characterised by deposition of polymeric IgA in the glomerulus with subsequent immune activation. Other patterns of glomerulonephritis include membranous nephropathy, where there is granular deposition of immunoglobulin on the glomerular capillary basement membrane. Systemic autoimmune diseases such as systemic lupus erythematosus can cause a variety of types of glomerulonephritis. Finally, some chronic forms of glomerulonephritis are pauci-immune, that is they have no immune deposition. This is seen in focal and segmental glomerulosclerosis.

Lower urinary tract disease

A variety of differing pathologies make up this group and together they represent 5–10% of all cases of CKD. The conditions include the following.

Reflux disease

This results from reflux of urine back up the renal tract towards the kidneys. This can result in recurrent infections and subsequent scarring.

Renal stone disease

Kidney stones are primarily formed of calcium oxalate and calcium phosphate. They can cause urinary tract obstruction and infection.

Chronic pyelonephritis

Recurrent urinary tract infection can result in renal scarring; this is often in the context of reflux disease but may occur without it.

Extrinsic renal tract obstruction

In males, the commonest cause of this is prostatic hypertrophy though there are many other causes.

Hereditary/congenital diseases

There are many inherited renal diseases and together they represent 5% of CKD cases. It is, however, important to remember that they make up a higher proportion of cases of end stage renal disease. The commoner inherited conditions are APKD and Alport's syndrome. Autosomal dominant polycystic kidney disease is an inherited condition which results in the formation of multiple cysts in both kidneys throughout life. The kidneys become enlarged and frequently fail in middle age. Alport's syndrome is a disorder of glomerular basement membranes caused by a mutation affecting type IV collagen; X-linked, autosomal dominant and autosomal recessive forms of inheritance are all seen. The clinical manifestations include progressive nephritis with haematuria, proteinuria and sensorineural deafness.

Unknown cause

It is not uncommon for the cause of CKD to be unknown and this is the case in around 30% of patients who typically present with small kidneys and unremarkable immunological investigations. When the kidneys are small it is often not possible to carry out a renal biopsy or if possible the histology often shows severe scarring with no indication of the underlying cause.

Clinical manifestations

While uraemic symptoms are rare in CKD stage 4, they become more apparent as the patient approaches end stage renal disease. The onset of symptoms is slow and insidious so that patients may not realise that they are unwell. It is not uncommon for patients to present in end stage renal disease and require immediate dialysis at their first contact with the medical profession.

End stage renal disease is characterised by the requirement of renal replacement therapy to sustain life and it is often accompanied by uraemia, anaemia, acidosis, osteodystrophy, neuropathy and is frequently accompanied by hypertension, fluid retention and susceptibility to infection (Fig. 18.6). It results from a significant reduction in the excretory, homeostatic, metabolic and endocrine functions of the kidney that occur over a period of months or years.

In the following section, the clinical features of CKD are described, along with the pathogenesis.

Urinary tract features

Both polyuria and nocturia are found in CKD though neither is universal and many patients with CKD have no urinary symptoms. Proteinuria is common in CKD and can be present

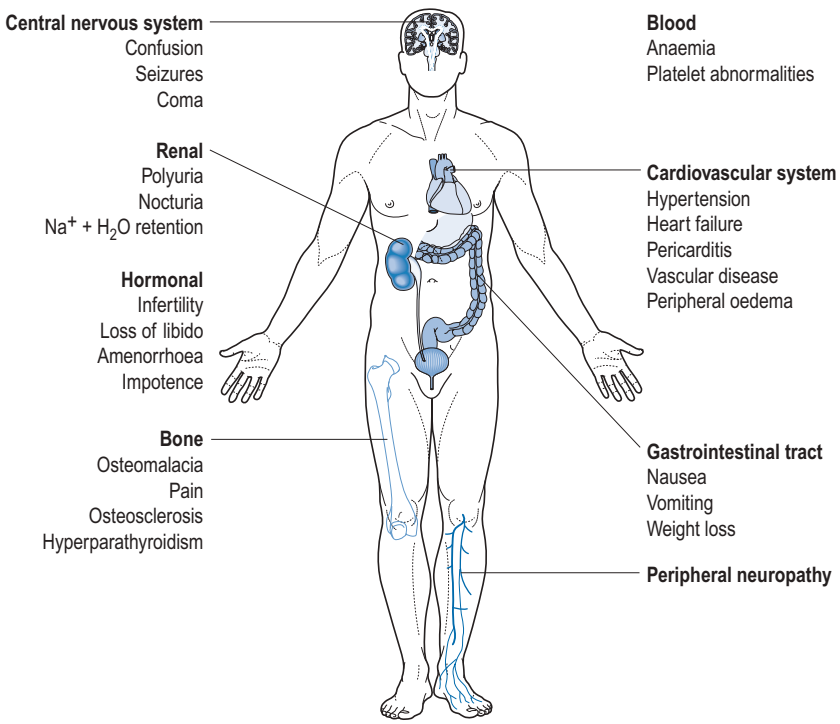

Fig. 18.6 Typical signs and symptoms of chronic kidney disease.

to varying degrees. Proteinuria is commonly measured using single urine samples to determine the albumin creatinine ratio (ACR). This method has almost entirely replaced the 24 h urine collection which was inconvenient and often unreliable. An ACR of 3-30 mg/mmol is described as microalbuminuria while in nephrotic-range proteinuria it is >250 mg/mmol. Haematuria may also be present and can reflect either glomerular or lower urinary tract pathology. The presence of blood and/or protein in the urine is described as an active urinary sediment. Whenever blood in the urine is detected an infection should be considered and excluded by urine microscopy for white cells and culture for organisms.

Polyuria and nocturia

Polyuria, where the patient frequently voids high volumes of urine, is often seen in CKD and results from medullary damage and the osmotic effect of a high serum urea level (>40 mmol/L). The ability to concentrate urine is also lost in CKD, which together with failure of physiological nocturnal antidiuresis, invariably results in nocturia, where the patient will be wakened two or three times a night with a full bladder.

Proteinuria

A degree of proteinuria is common in CKD and the prevalence of proteinuria increases with the severity of CKD. There are a number of precipitating factors including glomerular disease, failure of protein reabsorption in the tubules and rarely overflow of excess plasma proteins as seen in myeloma. Pronounced proteinuria (>1 g of protein in a 24-h collection, equivalent to an ACR >70 mg/mmol) usually indicates a glomerular aetiology. The presence and quantity of proteinuria are major determinants of progressive CKD.

Haematuria

Haematuria can be either macroscopic or microscopic; macroscopic haematuria is likely to result from lower urinary tract pathology (such as bladder lesions) and microscopic haematuria is most often of glomerular origin. Microscopy can identify the presence of casts which are also seen in glomerular diseases and allow the discrimination of the course of haematuria.

Hypertension and fluid overload

Most patients with CKD will have hypertension and this may be a cause or a consequence (or a combination of both) of their kidney disease. Furthermore, raised blood pressure may exacerbate renal damage and lead to accelerated deterioration of CKD.

Severe renal impairment leads to sodium retention, which in turn produces circulatory volume expansion with consequent hypertension. This form of hypertension is often termed 'salt-sensitive', as it may be exacerbated by salt intake. Lesser degrees of renal impairment reduce kidney perfusion, which activates renin production, with subsequent angiotensin-mediated vasoconstriction. Treatment of blood pressure, irrespective of choice of therapy, generally improves the course of CKD. As the GFR falls to very low levels the kidneys are unable to excrete salt and water adequately, resulting in the retention of extravascular fluid. All patients with fluid overload will by definition also have salt retention, even if this is not manifest in the serum sodium concentration.

Clinical findings

Eye damage in the form of hypertensive retinopathy may be found in those patients whose blood pressure has not been adequately controlled. This can be prevented by appropriate and timely antihypertensive therapy. Fluid retention can manifest as peripheral and pulmonary oedema and ascites. Oedema may be seen around the eyes on waking, the sacral region in supine patients and from the feet upwards in ambulatory patients. Volume-dependent hypertension occurs in about 80% of patients with CKD and becomes more prevalent as the GFR falls.

Uraemia

Many substances including urea, creatinine and water are normally excreted by the kidney and accumulate as renal function decreases. Some of the substances responsible for the toxicity of uraemia are intermediate in size between small, readily dialysed molecules and large non-dialysable proteins. These are described as 'middle molecules' and include phosphate, guanidines, phenols and organic acids. Clearly, there are a wide range of uraemic toxins but it is the blood level of urea that is often used to estimate the degree of toxin accumulation in uraemia. True symptomatic uraemia only occurs in very advanced CKD.

Clinical findings

The symptoms of uraemia include anorexia, nausea, vomiting, constipation, foul taste and skin discolouration that is presumed to be due to pigment deposition compounded by the pallor of anaemia. The characteristic complexion is often described as 'muddy', and is frequently associated with severe pruritus without an underlying rash. In extremely severe cases, crystalline urea is deposited on the skin (uraemic frost).

In uraemia, there is also an increased tendency to bleed, which can exacerbate pre-existing anaemia because of impaired platelet adhesion and modified interaction between platelets and blood vessels resulting from altered blood rheology.

Anaemia

Anaemia is a common consequence of CKD and affects most people with CKD stages 4 and 5. The fall in haemoglobin level is a slow, insidious process accompanying the decline in renal function. A normochromic, normocytic pattern is usually seen with haemoglobin levels falling to around 8 g/dL by end stage renal disease.

Several factors contribute to the pathogenesis of anaemia in CKD, including shortened red cell survival, marrow suppression by uraemic toxins and iron or folate deficiency associated with poor dietary intake or increased loss, for example, from gastro-intestinal bleeding. However, the principal cause results from damage of peritubular cells leading to inadequate secretion of erythropoietin. This hormone, which is produced mainly, although not exclusively, in the kidney, is the main regulator of red cell proliferation and differentiation in bone marrow. Hyperparathyroidism also reduces erythropoiesis by damaging bone marrow and therefore exacerbates anaemia associated with CKD. The RAAS is also involved in erythropoiesis since renin increases erythropoietin production and this explains how ACE inhibitors can cause small reductions in haemoglobin.

Clinical findings

Anaemia in CKD is a major cause of fatigue, breathlessness at rest and on exertion, lethargy and angina. Patients may also complain of feeling cold, poor concentration and reduced appetite and libido. Compensatory haemodynamic changes occur with CKD, cardiac output is increased to improve oxygen delivery to tissues, although this may result in tachycardia and palpitations. The anaemia of CKD usually responds to treatment with erythropoietin-stimulating agents (ESAs).

Bone disease (renal osteodystrophy)

Renal osteodystrophy describes the four types of bone disease associated with CKD:

- secondary hyperparathyroidism
- osteomalacia (reduced mineralisation)
- mixed renal osteodystrophy (both hyperparathyroidism and osteomalacia)
- adynamic bone disease (reduced bone formation and resorption).

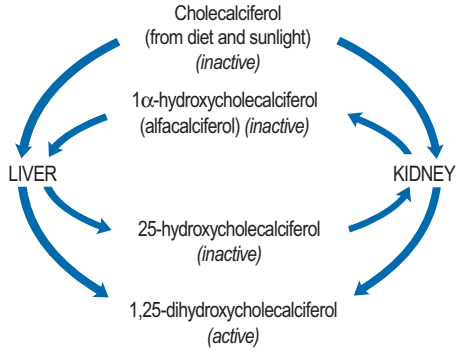

Fig. 18.7 Renal and hepatic involvement in vitamin D metabolism.

Cholecalciferol, the precursor of active vitamin D, is both absorbed from the gastro-intestinal tract and produced in the skin by the action of sunlight. Production of active vitamin D, 1,25-dihydroxycholecalciferol (calcitriol), requires the hydroxylation of the colecalciferol molecule at both the 1α and the 25 position (Fig. 18.7).

Hydroxylation at the 25 position occurs in the liver, while hydroxylation of the 1α position occurs in the kidney; this latter process is impaired in renal failure. The resulting deficiency in vitamin D leads to defective mineralisation of bone and subsequent osteomalacia which is almost inevitable in those with CKD stage 3 and beyond.

The deficiency in vitamin D with the consequent reduced calcium absorption from the gut in combination with the reduced renal tubular reabsorption results in hypocalcaemia (Fig. 18.8).

These disturbances are compounded by hyperphosphataemia caused by reduced phosphate excretion, which in turn reduces the concentration of ionised serum calcium by sequestering calcium phosphate in bone and in soft tissue. Hypocalcaemia, hyperphosphataemia and a reduction in the direct suppressive action of 1,25-dihydroxycholecalciferol on

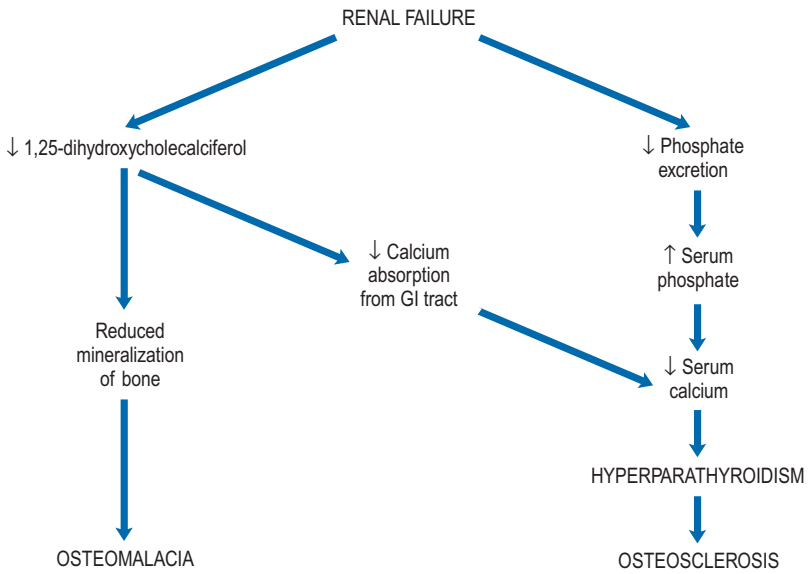

Fig. 18.8 Disturbance of calcium and phosphate balance in chronic renal failure.

the parathyroid glands results in an increased secretion of parathyroid hormone (PTH).

Since the failing kidney is unable to respond to PTH by increasing renal calcium reabsorption, the serum PTH levels remain persistently elevated, and hyperplasia of the parathyroid glands occurs. The resulting secondary hyperparathyroidism produces a disturbance in the normal architecture of bone and this is termed osteosclerosis (hardening of the bone). A further possible consequence of secondary hyperparathyroidism produced in response to hypocalcaemia is that sufficient bone reabsorption may be caused to maintain adequate calcium levels. This, in combination with hyperphosphataemia, may result in calcium phosphate deposition and soft tissue calcification.

Clinical findings

Bone pain is the main symptom, and distinctive appearances on radiography may be observed, such as 'rugger-jersey' spine, where there are alternate bands of excessive and defective mineralisation in the vertebrae (Fig. 18.9).

Neurological changes

The most common neurological changes are non-specific and include inability to concentrate, memory impairment, irritability and stupor probably caused by uraemic toxins.

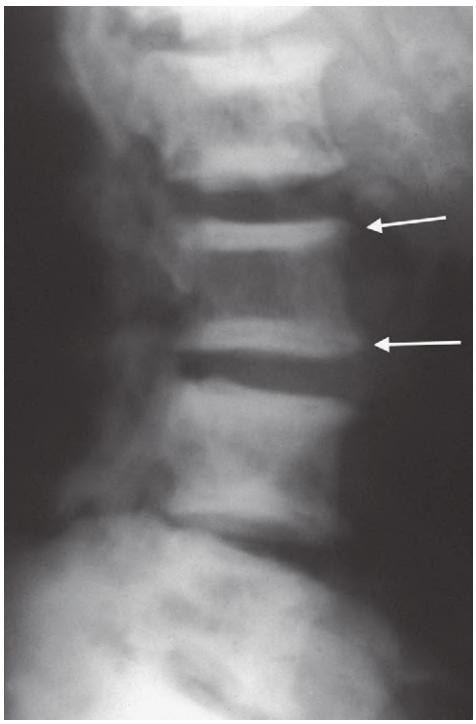

Fig. 18.9 Lateral radiograph of the spine in a patient with chronic renal failure. Characteristic endplate sclerosis (arrows) are referred to as 'rugger-jersey spine' (reproduced by kind permission of Dr M. J. Kline, Department of Diagnostic Radiology, Cleveland Clinic Foundation).

Clinical features

Fits owing to cerebral oedema or hypertension may occur. A 'glove and stocking' peripheral neuropathy can occur as can mono-neuritis multiplex.

Muscle function

Muscle symptoms are probably caused by general nutritional deficiencies and electrolyte disturbances, notably of divalent cations and especially by hypocalcaemia.

Clinical findings

Muscle cramps and restless legs are common and may be major symptoms causing distress to patients, particularly at night. Rarely a proximal myopathy of shoulder and pelvic girdle muscles may develop.

Electrolyte disturbances

Since the kidneys play such a crucial role in the maintenance of volume, extracellular fluid composition and acid–base balance, it is not surprising that disturbances of electrolyte levels are seen in CKD.

Sodium

Serum sodium levels can be relatively normal even when creatinine clearance is very low. However, patients may exhibit hypo- or hypernatraemia depending upon the condition and therapy employed (see Table 18.3).

Table 18.3 Causes and mechanism of serum sodium abnormalities in chronic kidney disease

	Mechanism	Cause/effect
Hypernatraemia	Sodium overload	Drugs, for example, antibiotic sodium salts
	Hypotonic fluid loss	Osmotic diuresis
		Sweating
	↓ Water intake	Unconsciousness
Hyponatraemia	Dilution by intracellular water movement	Mannitol
Hyperglycaemia	Water overload	Acute dilution by intravenous fluids, for example, 5% dextrose infusion
		Excessive intake
		Congestive cardiac failure
		Nephrotic syndrome

Potassium

Potassium levels can be elevated in CKD. Hyperkalaemia is a potentially dangerous condition as the first indication of elevated potassium levels may be life-threatening cardiac arrest. Potassium levels of over 7.0 mmol/L are life-threatening and should be treated as an emergency. Hyperkalaemia may be exacerbated in acidosis as potassium shifts from within cells.

ECG changes accompany any rise in serum potassium and become more pronounced as levels increase. T waves peak ('tenting'), there is a reduction in the size of P waves, an increase in the PR interval and a widening of the QRS complex. P waves eventually disappear and the QRS complex becomes even wider. Ultimately, the ECG assumes a sinusoidal appearance prior to cardiac arrest (see Fig. 18.10).

Hydrogen ions

Hydrogen ions (H^+) are a common end-product of many metabolic processes and about 40–80 mmol are normally excreted via the kidney each day. In renal failure, H^+ is retained, causing acidosis; the combination of H^+ with bicarbonate (HCO^{3-}) results in the removal of some hydrogen as water, the elimination of carbon dioxide via the lungs, and a reduction in serum bicarbonate level.

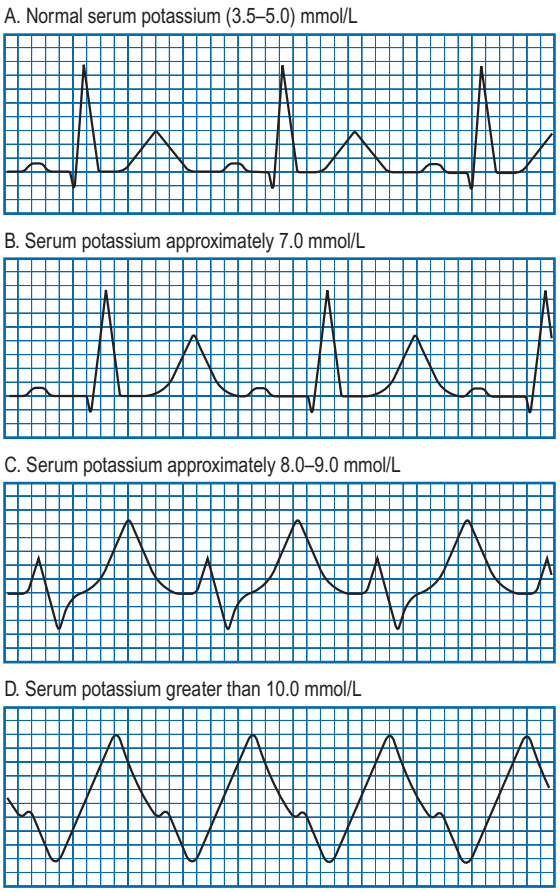

Fig. 18.10 Typical ECG changes in hyperkalaemia.

Diagnosis, investigations and monitoring

Although the diagnosis of CKD may be suspected because of signs and symptoms of renal disease, more often it is discovered incidentally. There are patients with CKD for whom no cause can be identified, often because they have two small kidneys which are not safe to biopsy. This appearance results from damage at some unspecified time in the past.

Family, drug and social histories are all important in elucidating the causes of renal failure, since genetics or exposure to toxins, including prescription, over-the-counter and herbal drugs, might be implicated.

Physical examination may be helpful. Signs of anaemia and skin pigmentation, excoriations owing to scratching and whitening of the skin with crystalline urea ('uraemic frost') may point to severe disease. Palpable or audible bruits over the femoral arteries are strongly associated with extensive arteriosclerosis and are commonly found in patients with renal vascular disease. Ankle oedema and a raised jugular venous pressure suggest fluid retention and in severe CKD a fishy smell on the breath known as 'uraemic foetor' is characteristic. In some patients, the kidneys may be palpable. Large irregular kidneys are indicative of polycystic disease, whereas smooth, tender enlarged kidneys are likely to be infected or obstructed. However, in the large majority of CKD the kidneys are small and are impalpable. A palpable bladder suggests outflow tract obstruction which is often due to prostatic hypertrophy in men.

Functional assessment of the kidney may be performed by testing serum and urine. The serum creatinine level is a more reliable indicator of renal function than the serum urea level though both are normally measured. Hyperkalaemia, acidosis with a correspondingly low serum bicarbonate level, hypocalcaemia and hyperphosphataemia are frequently present and can help to differentiate a new presentation of CKD from AKI.

Urine should be examined visually and microscopically and urinalysis performed for assessment of urinary sediment and a spot urine assessment of the ACR. The patient may report a change in urine colour, which might result from blood staining by whole cells or haemoglobin, drugs or metabolic breakdown products. Urine may also appear milky after connection with lymphatics, cloudy following infection, contain solid material such as stones, crystals, casts, or froth excessively in proteinuria.

Dipstick tests enable simple, rapid estimation of a wide range of urinary parameters including pH, specific gravity, leucocytes, nitrites, glucose, blood and protein. Positive results should, however, be quantified by more specific methods.

Structural assessments of the kidney may be performed using a number of imaging procedures, including:

- ultrasonography
- intravenous urography (IVU)
- plain abdominal radiography
- computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA).

Ultrasonography

This method produces two dimensional images using sound waves and is used as the first-line investigational tool in many hospitals. The technique is harmless, non-invasive, quick, inexpensive, enables measurements to be made and produces images in real time. The latter feature allows accurate and safe positioning of biopsy needles. Ultrasonography is particularly useful in the differentiation of renal tumours from cysts and in the assessment of renal tract obstruction. Doppler ultrasonography is a development that enables measurement of flow rate and direction of the intra- and extrarenal blood supply.

Intravenous urography

IVU is now used very infrequently because it uses high doses of radiation and contrast media, newer modalities such as CT scanning can provide more information. Timed serial radiographs are taken of the kidneys and the full length of the urinary tract following an intravenous injection of an iodine-based contrast medium that is filtered and excreted by the kidney. IVU will show the following:

- the presence, length and position of the kidneys; in CKD the kidneys generally shrink in proportion to nephron loss, the exception being the enlarged kidneys seen in polycystic disease
- the presence or absence of renal scarring and the shape of the calices and renal pelvis; renal cortical scarring and caliceal distortion indicate chronic pyelonephritis
- obstruction to the ureters, for example, by a stone, tumour or retroperitoneal fibrosis; these require surgical intervention
- the shape of the bladder and the presence of residual urine; enlargement and a post-micturition residue suggest urethral obstruction such as prostatic hypertrophy.

Nuclear medicine investigations

There are two commonly used nuclear medicine investigations, the first uses mercapto acetyl tri-glycerine (MAG3). This is used for assessment of renal perfusion and the identification of outflow obstruction. The other is a dimercapto succinic acid (DMSA) scan, the purpose of which is to ascertain the percentage that each kidney contributes to overall function.

The similar techniques of CT and MRI provide excellent structural information about the kidneys and urinary tract. They use less radiation (none in the case of MRI) and less contrast media than an IVU, although the machinery required is more expensive than that needed for traditional imaging methods. CT is particularly useful in the investigation of kidney stones, where it has superseded the IVU. MRA can also give information about renal blood supply; however, in recent years, concerns have arisen about the use of gadolinium as a contrast agent used in MRA. This has been associated with nephrogenic systemic fibrosis which results in death in a proportion of patients; those with CKD stages 4 and 5 are at highest risk of developing this condition. While the use of gadolinium is not contraindicated in this group, it must be used with great care and protocols will vary from unit to unit.

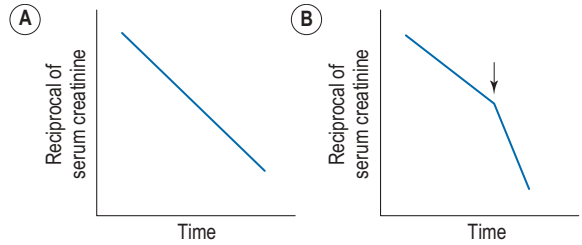

Fig. 18.11 Stylised reciprocal creatinine plots. (A) Linear, uniform progression in the decline in renal function. (B) Sudden decline in renal function (arrow).

Renal biopsy

If imaging techniques fail to give a cause for the reduction in renal function, a renal biopsy may be performed, although in advanced disease extensive scarring of the renal tissue may obscure the original (primary) diagnosis. Also, the small shrunken kidneys often seen in CKD are difficult to biopsy and may subsequently bleed. Most clinicians do not biopsy in this setting. In patients whose GFR is below 30 mL/min, injection of vasopressin (ADH) might minimise bleeding following renal biopsy, although evidence for this is limited and use is not widespread.

Graphical plots of glomerular filtration rate

All patients with CKD should have their serum biochemistry and haematology monitored regularly to detect any of the sequelae of the disease. In some patients with CKD, the decline in renal function progresses at a constant rate and may be monitored by plotting the estimated GFR against time (Fig. 18.11). The intercept with the *x*-axis indicates the time at which renal function will fall to zero and can be used to predict when the GFR will reach approximately 10 mL/min, that is, the level at which renal replacement therapy should be initiated (Fig. 18.11A). If an abrupt decline in the slope of the reciprocal plot is noted (Fig. 18.11B), this indicates a worsening of the condition or the presence of an additional renal insult. The cause should be detected and remedied if possible. It is, however, increasingly recognised that most patients with CKD do not sustain a predictable decline. Many stabilise or follow a path of episodes of accelerated decline followed by months or years of stability. These observations are of great interest and are an increasing focus of clinical research.

Prognosis

When the GFR has declined to about 20 mL/min, a continuing deterioration in renal function to end stage renal disease is common even when the initial cause of the kidney damage has been

removed and appropriate treatment instigated. The mechanisms for the decline in renal function include uncontrolled hypertension, proteinuria and damage resulting from hyperfiltration through the remaining intact nephrons. Serial GFR measurements should be monitored in conjunction with the patient's clinical condition to ensure the detection of the most appropriate point at which to commence renal replacement therapy. When a patient reaches an eGFR of 20 mL/min, plans should be in place for choice of renal replacement modality, transplantation or conservative management and where appropriate ongoing management of anaemia and bone disease.

Treatment

The aims of the treatment of CKD can be summarised as follows:

- Reverse or arrest the process causing the renal damage (this may not be possible)
- Avoid conditions that might worsen renal failure (Box 18.1)
- Treat the secondary complications of CKD (renal anaemia and bone disease)
- Relieve symptoms
- Implement regular dialysis treatment and/or transplantation at the most appropriate time.

Reversal or arrest of primary disease

By definition, CKD rarely has a readily reversible component, in contrast to acute renal failure. However, it is sometimes possible to identify a disease specific factor that is contributing to declining renal function and remove it. A postrenal lesion such as a ureter obstructed by a stone or a ureteric tumour may be successfully treated surgically. Glomerulonephritis may respond to immunosuppressants and/or steroids. Clearly, when drug-induced renal disease is suspected the offending agent should be stopped. These factors predominantly cause acute renal failure but they can cause acute on chronic failure and their reversal may prevent further deterioration.

Hypertension

Optimum control of blood pressure is one of the most important therapeutic measures since there is a vicious cycle of events whereby hypertension causes damage to the intrarenal vasculature resulting in thickening and hyalinisation of the walls of arterioles and small vessels. This damage effectively reduces renal perfusion, contributing to stimulation of the RAAS. Arteriolar vasoconstriction, sodium and water retention result, which in turn exacerbates the hypertension.

Antihypertensive therapy with certain agents might produce a transient reduction in GFR over the first 3 months of treatment as the systemic and glomerular blood pressure drop; this is mainly seen with ACE inhibitors/angiotensin receptor blockers (ARBs). However, it is possible to ultimately halt or slow the decline in many cases.

The drugs used to treat hypertension in renal disease are generally the same as those used in other forms of hypertension, although allowance must be made for the effect of renal failure on drug disposition (NICE, 2008).

Box 18.1 Factors that might exacerbate established chronic renal failure

Reduced renal blood flow
Hypotension
Hypertension
Nephrotoxins including drugs
Renal artery disease
Obstruction, for example, prostatic hypertrophy

Calcium channel blockers

For patients without proteinuria, calcium channel blockers (CCBs) are the agents of choice. They produce vasodilatation principally by reducing Ca^{2+} influx into vascular muscle cells. CCBs also appear to promote sodium excretion in hypertension associated with fluid overload. The mechanism is unclear but may relate to the finding that high sodium levels can cause vasoconstriction by interfering with calcium transport.

Both verapamil and diltiazem (non-dihydropyridine CCBs) block conduction across the atrioventricular node and should not be used in conjunction with β-blockers. They are also negative cardiac inotropes. By contrast, dihydropyridines such as nifedipine and amlodipine produce less cardiac depression and differentially dilate afferent arterioles in the kidney. In theory, dihydropyridines can, therefore, cause intraglomerular hypertension and glomerular damage despite decreased systemic hypertension, the relevance of this to the history of CKD is uncertain.

CCBs can produce headache, facial flushing and oedema. The latter can be confused with the symptoms of volume overload but is resistant to diuretics. The mechanism via which these effects occur is related to a change in pre-capillary hydrostatic pressure, which forces fluid into the interstitial compartment. The oedema is not related to salt or water retention; hence, the lack of response to diuretic therapy.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The role of ACE inhibitors in hypertensive patients with renal insufficiency is complicated, the current evidence base supports the principle that all diabetic patients with micro/macroalbuminuria and CKD should be treated with ACE inhibitors or ARBs regardless of blood pressure. There is also evidence that in non-diabetic patients with proteinuria, the use of these drugs can reduce proteinuria and thus reduce progression of CKD. ACE inhibitors reduce circulating angiotensin II and ARBs block binding to the angiotensin II receptor, which results in vasodilatation and reduced sodium retention.

These agents can produce a reduction in GFR by preventing the angiotensin II mediated vasoconstriction of the

efferent glomerular arteriole. This contributes to the high-pressure gradient across the glomerulus, which is responsible for filtration and intra-glomerular hypertension. This problem may only be important in patients with renal vascular disease, particularly those with functionally significant renal artery stenoses where they should be avoided.

ACE inhibitors and ARBs preferentially protect the glomerulus over and above their effect as systemic hypertensive agents, through decreasing efferent glomerular arteriolar vasoconstriction and therefore intra-glomerular hypertension and hyperfiltration. Whilst the evidence for use of these drugs in patients with diabetic renal disease and proteinuric non-diabetic CKD is clear, care must be exercised in the following settings:

- Patients who sustain an early decline (in the first 7–10 days after ACE inhibitors/ARBs commencement) in kidney function. The drug should be stopped and potential renal artery stenosis investigated.
- Patients with non-proteinuric, non-diabetic CKD. These agents are overused in this setting. There is no evidence that they provide a real renal benefit over other anti-hypertensive drugs.
- Patients with an accelerated decline in kidney function in the months to years after commencement of ACE inhibitors/ARBs. This is increasingly described and may reflect a resetting of the intra-renal perfusion to a level that potentiates chronic renal ischaemia present in most cases of CKD irrespective of cause.
- Patients with an intercurrent acute illness, particularly those admitted to hospital. Hypotension or infection will put patients at an increased risk of AKI.

For long-term management, it is usually preferable to use an agent with a duration of action that permits once-daily dosing. There is little to choose clinically between the ACE inhibitors currently on the market; however, consideration should be given to the cost benefits of choosing an agent that does not require dose adjustment in renal failure.

It has been reported that ACE inhibitors may reduce thirst, which may be useful in those patients who have a tendency to fluid overload as a result of excessive drinking. ACE inhibitors are potassium sparing and therefore serum potassium should be monitored carefully. A low-potassium diet may be necessary.

ARBs have properties similar to ACE inhibitors with the advantage that, since they do not inhibit the breakdown of kinins such as bradykinin, they do not cause the dry cough associated with the ACE inhibitors. There is interest in the potential use of dual blockade of the RAAS using ACE inhibitors and ARBs to produce more complete blockade of angiotensin II. However, evidence to date has shown no added benefit and some evidence of adverse renal outcomes.

The observation that patients treated with ACE inhibitors initially have lower circulating angiotensin II but then experienced a rise in angiotensin II, known as the escape phenomenon, led to the expectation that dual blockade with ACE inhibitors and ARBs would resolve this. This has not been the case in practice and other solutions to this problem have been sought. Renin is the rate-limiting enzyme of the RAAS, and it has been suggested that interruption at this stage should provide complete RAAS blockade. The direct renin inhibitors (DRIs) are a new class of antihypertensive and the early evidence suggests a greater benefit when combined with an ARB than when used as monotherapy.

Diuretics

Diuretics are of use in patients with salt and volume overload, which is usually indicated by the presence of oedema. This type of hypertension may be particularly difficult to treat. The choice of agent is generally limited to a loop diuretic. Potassium sparing diuretics are usually contraindicated owing to the risks of developing hyperkalaemia, and thiazides become ineffective as renal failure progresses. In combination with ACE inhibitors, spironolactone can significantly reduce proteinuria; however, the combination of these agents clearly raises the risk of significant hyperkalaemia and care must be taken (Bianchi et al., 2005). The combination should be avoided when the eGFR falls to <30 mL/min.

As loop diuretics need to be filtered to exert an action, progressively higher doses are required as CKD worsens. Doses of more than 250 mg/day of furosemide may be required in advanced renal failure. Patients who do not respond to oral loop diuretic therapy alone may benefit from concomitant administration of metolazone, which acts synergistically to produce a profound diuresis. Alternatively, the loop diuretic may be given intravenously. Care must be taken to avoid hypovolaemia (by monitoring body weight) and electrolyte disturbances such as hypokalaemia and hyponatraemia.

Thiazide diuretics, with the notable exception of metolazone, are ineffective at a low GFR and may accumulate, causing an increased incidence of side effects.

β-Blockers

β-Blockers are commonly used in the treatment of hypertension in CKD. They exhibit a range of actions including a reduction of renin production. Consequently, β-blockers have a particular role in the rational therapy of hypertension without fluid overload. However, β-blockers can reduce cardiac output, cause peripheral vasoconstriction and exacerbate peripheral vascular disease.

It is advisable to use the more cardioselective β-blockers atenolol or metoprolol. Atenolol is excreted renally and consequently should require dosage adjustment in renal failure. In practice, however, atenolol is effective and tolerated well by renal patients at standard doses. However, metoprolol is theoretically a better choice since it is cleared by the liver and needs no dosage adjustment, although small initial doses are advised in renal failure since there may be increased sensitivity to its hypotensive effects.

Selective α1-blockers

These vasodilators produce a variety of actions that may be of benefit in hypertension associated with CKD. Sympathetic adrenergic activity can lead to sodium retention. Selective

α_1-blockers have also been shown to produce improvements in insulin sensitivity, adverse lipid profiles and obstruction caused by hypertrophy of the prostate, all of which might be associated with some forms of CKD. These agents are used less commonly since there is some evidence that, in comparison to other antihypertensives, use is associated with adverse cardiovascular outcomes, especially the development of heart failure.

Vasodilators

The vasodilators hydralazine and minoxidil have been used to treat hypertension in CKD with varying degrees of success but are usually only used when other measures inadequately control blood pressure. The sensitivity of patients to these drugs is often increased in renal failure, so, if used, therapy should be initiated with small doses. These agents cause direct peripheral vasodilation with resultant reflex tachycardia, which may require suppression by co-prescription of a β-blocker.

Centrally acting drugs

Methyldopa and clonidine are not commonly used as antihypertensives in CKD because of their adverse side effect profiles. If they are used in renal failure, initial doses should be small because of increased sensitivity to their effects.

Spironolactone

The potassium sparing diuretic spironolactone is an aldosterone receptor antagonist, and it is through this effect that it reduces proteinuria. Studies have suggested that it may be additionally effective in combination with either an ACE inhibitor or an ARB but not as triple therapy. Care needs to be taken to avoid hyperkalaemia in patients on these regimens.

Statins

Statins are known to have beneficial effects on endothelial function, improving renal perfusion while reducing abnormal permeability to plasma proteins. However, statins are not indicated for delaying the progression of CKD but are currently used for conventional indications only in such patients.

Management of symptoms associated with CKD

Gastro-intestinal symptoms

Nausea and vomiting may persist after starting a low-protein diet. Metoclopramide is useful to treat this, but sometimes accumulation of the drug and its metabolites may occur, leading to extrapyramidal side effects. Patients should be started on a low dose, which should then be increased slowly. Prochlorperazine or cyclizine may also be useful. The 5-HT_3 antagonists such as ondansetron have also been shown to be effective. The anaemic patient often becomes less nauseated when treated with an erythropoiesis stimulating agent.

Constipation is a common problem in patients with renal disease, partly as a result of fluid restriction and anorexia and partly as a consequence of drug therapy with agents such as phosphate binders. It is particularly important that patients managed with peritoneal dialysis do not become constipated, as this can reduce the efficacy of dialysis. Conventional laxative therapy may be used, such as bulk-forming laxatives or increased dietary fibre for less severe constipation. Alternatively, a stimulant such as senna with enemas or glycerine suppositories may be used for severe constipation. Higher doses of senna, typically 2–4 tablets at night, may be required. It should be noted that certain brands of laxatives that contain ispaghula husk may also contain significant quantities of potassium, and should be avoided in renal failure because of the risk of hyperkalaemia. Sterculia preparations are an effective alternative.

Pruritus

Itching associated with renal failure can be extremely severe, distressing and difficult to treat. It can also be disfiguring as a result of over-enthusiastic scratching. The exact mechanism responsible for the itching is not clear and several possibilities have been suggested including: xerosis (dry skin), skin micro-precipitation of divalent ions, elevated PTH levels and increased dermal mast cell activity. Generally, however, no underlying cause is found and it is likely that a multifactorial process is responsible.

Sometimes correction of serum phosphate or calcium levels improves the condition, as does parathyroidectomy. Conventionally, oral antihistamines are used to treat pruritus; however, topical versions should not be used owing to the risk of allergy. Non-sedating antihistamines such as loratidine are generally less effective than sedating antihistamines such as chlorphenamine or alimemazine which may be useful, particularly at night. Topical crotamiton lotion and creams may also be useful in some patients. Other non-drug therapies include either warming or cooling the skin using baths, three times weekly, UVB phototherapy and modified electrical acupuncture.

Dietary modifications for uraemic symptoms

Although urea is only one of the toxins encountered in uraemia, many patients experience a symptomatic improvement when dietary protein intake is reduced, presumably through a reduction in the output of nitrogenous waste. There is some evidence that, as well as reducing the symptoms of uraemia, protein restriction slows the progression of CKD, but this remains controversial. Protein-restricted diets have been used extensively in the past but they are unpalatable and the benefits marginal, so they are used infrequently in modern medical practice.

Dietary modifications in CKD

Low protein diets have already been discussed. Other dietary modifications include sodium and fluid restriction to reduce the risk of fluid overload, potassium restriction to reduce the risk of hyperkalaemia and vitamin supplementation. The dietary restrictions for patients with CKD can be arduous and difficult to follow.

Fluid retention

Oedema may occur as a result of sodium retention and the resultant associated water retention. Patients with CKD may also have hypoalbuminaemia following renal protein loss, and this can result in an osmotic extravasation of fluid and its retention in tissues. By end stage renal disease pulmonary and peripheral oedema is best controlled with dialysis but diuretics can be useful. The daily fluid intake should be restricted to between one and three litres, depending upon the volume of urine produced by the patient (if any). It is important to note that the fluid allowance must include fluids ingested in any form, including sauces, medicines and fruits, in addition to drinks. The fluid restriction is very difficult to maintain. Sucking ice cubes may relieve an unpleasantly dry mouth, but patients should be encouraged not to swallow the melted water.

Sodium restriction. Sodium intake can be reduced to a satisfactory level of 80 mmol/day by avoiding convenience foods and snacks or the addition of salt to food at the table. This is usually tolerable to patients. It is important to be aware of the contribution of sodium-containing medication, including some antibiotics, soluble or effervescent preparations, magnesium trisilicate mixture, Gaviscon, sodium bicarbonate and the plasma expanders hetastarch and gelatin.

Potassium restriction. Hyperkalaemia often occurs in CKD and may cause life-threatening cardiac arrhythmias. If untreated, asystolic cardiac arrest and death may result. Patients are often put on a potassium-restricted diet by avoiding potassium-rich foods such as fruit and fruit drinks, vegetables, chocolate, beer, instant coffee and ice cream. Many medicines have a high potassium content, for example, potassium citrate mixture, some antibiotics and ispaghula husk sachets. The use of these drugs is less of a problem in dialysed patients. Emergency treatment is necessary if the serum potassium level is above 7.0 mmol/L or if there are ECG changes. The most effective treatment is dialysis but if this is not available other measures may be tried (see Chapter 17).

The rationale and necessity for a renal diet and fluid restriction can be difficult for a patient to understand and adherence may be a problem. Consequently, the involvement of a specialist renal dietician can be valuable in optimising dietary therapies.

Anaemia

The normochromic, normocytic anaemia of CKD does not respond to iron or folic acid unless there is a coexisting deficiency. Traditionally, the only treatment available was to give red blood cell transfusions, but this is time-consuming, expensive, an infection risk, may lead to fluid and iron overload and promotes antibody formation, which may give problems if transplantation is subsequently attempted. The introduction of ESAs, initially as recombinant human erythropoietins (epoetin alfa and beta) have transformed the management of renal anaemia. Epoetin alfa and beta were thought to be indistinguishable in practical terms, as well as being immunologically and biologically indistinguishable from physiological erythropoietin. However, it has now been recognised that epoetins can be associated with the production of anti-erythropoietin antibodies leading to a severe anaemia which is unresponsive to exogenous epoetin. This is known as pure red cell aplasia (PRCA) and is more commonly associated with epoetin alfa when given by the subcutaneous route. The subcutaneous route is preferred as it provides equally effective clinical results while using similar or smaller doses (up to 30% less) when given three times a week. Most patients report a dramatically improved quality of life after starting epoetin therapy.

Darbepoetin alfa is a novel erythropoiesis-stimulating protein (NESP) that is a recombinant hyperglycosylated analogue of epoetin which stimulates red blood cell production by the same mechanism as the endogenous hormone. The terminal half-life in man is three times longer than that of epoetin and consequently requires a once weekly or alternate weekly dosing schedule. Recently, a longer acting ESA has been introduced (methoxy polyethylene glycol-epoetin beta, pegzerepoetin alfa). This is a continuous erythropoietin receptor activator (CERA), which can be used in a once monthly dosing schedule.

Iron and folate deficiencies must be corrected before therapy is initiated, while patients receiving epoetin generally require concurrent iron supplements because of increased marrow requirements. Supplemental iron is often given intravenously owing to bioavailability problems with oral forms. Maintaining iron stores ensures the effect of epoetin is optimised for minimum cost, as with insufficient iron stores a patient will not respond to treatment with epoetin.

Epoetin therapy should aim to achieve a slow rise in the haemoglobin concentration to avoid cardiovascular side effects associated with a rapidly increasing red cell mass, such as hypertension, increased blood viscosity/volume, seizures and clotting of vascular accesses. Blood pressure should be closely monitored.

An initial subcutaneous or intravenous epoetin dose of 50 units/kg body-weight three times weekly, increased as necessary in steps of 25 units/kg every 4 weeks, should be given to produce a haemoglobin increase of not more than 2 g/dL per month. The target haemoglobin concentration is commonly 10.5–12.5 g/dL with most aiming for a target around 11.5 g/dL. Once this has been reached, a maintenance dose of epoetin in the region of 33–100 units/kg three times a week or 50–150 units/kg twice weekly should maintain this level.

There have been several studies of ESAs which have shown an increased risk of cardiovascular morbidity and overall mortality in people treated to a target >12.5 g/dL (Phrommintikul

et al., 2007). This has lead to more conservative dosing strategies and prompt discontinuation or reduction of dose in patients with Hb >12.5 g/dL.

Correcting anaemia usually helps control the symptoms of lethargy and myopathy, and often greatly reduces nausea. Improved appetite on epoetin therapy can, however, increase potassium intake, and may necessitate dietary control.

Acidosis

Since the kidney is the main route for excreting H^+ ions, CKD may result in a metabolic acidosis. This will cause a reduction in serum bicarbonate that may be treated readily with oral doses of sodium bicarbonate of 1–6 g/day. As the dose of bicarbonate is not critical, it is easy to experiment with different dosage forms and strengths to suit individual patients. If acidosis is severe and persistent then dialysis may be required. Correction of acidosis may slow the decline in renal function.

Neurological problems

Neurological changes are generally caused by uraemic toxins and improve on the treatment of uraemia by dialysis or diet. Muscle cramps are common and are often treated with quinine sulphate. Restless legs may respond to low doses of clonazepam or co-careldopa.

Osteodystrophy

The osteodystrophy of renal failure is due to three factors: hyperphosphataemia, vitamin D deficiency and hyperparathyroidism.

Hyperphosphataemia

The management of hyperphosphataemia depends initially upon restricting dietary phosphate. This can be difficult to achieve effectively, even with the aid of a specialist dietician, because phosphate is found in many palatable foods such as dairy products, eggs, chocolate and nuts. Phosphate-binding agents can be used to reduce the absorption of orally ingested phosphate in the gut, by forming insoluble, non-absorbable complexes when taken a few minutes before or with meals. Traditionally, phosphate-binders were usually salts of a di- or trivalent metallic ion, such as aluminium, calcium or occasionally magnesium. Whilst calcium containing phosphate binders remain in widespread use, sevelemar and lanthanum-based binders are increasingly used.

Calcium acetate is widely used as a phosphate binder. The capacity of calcium acetate and calcium carbonate to control serum phosphate appears similar. However, phosphate control is achieved using between half and a quarter of the dose of elemental calcium when calcium acetate is used. Whether this translates to a decreased likelihood of producing unwanted hypercalcaemia with calcium acetate therapy is as yet unclear.

Calcium carbonate has been used as a phosphate binder. Unfortunately, it is less effective as a phosphate binder than aluminium, and sometimes requires doses of up to 10 g daily. Calcium carbonate has advantages, however, in that correction of concurrent hypocalcaemia can be achieved.

Sevelamer, a hydrophilic but insoluble polymeric compound is used increasingly as a phosphate binder. Sevelamer binds phosphate with an efficacy similar to calcium acetate but with no risk of hypercalcaemia. Mean levels of total and low-density cholesterol are also reduced with sevelamer use. This compound does not appear to present any risk of toxicity but may cause bowel obstruction and is relatively expensive when compared to other phosphate binders.

Lanthanum, like sevelamer, is a non-calcium containing phosphate binder; there is therefore no resultant risk of hypercalcaemia but there are gastro-intestinal side effects and the drug is significantly more expensive than the alternatives. While both of the non-calcium containing phosphate binders available have been shown to reduce phosphate levels and keep calcium within acceptable levels, no improvements in cardiovascular endpoints have been demonstrated to date.

Historically, aluminium hydroxide was widely used as a phosphate binder owing to the avid binding capacity of aluminium ions. However, a small amount of aluminium may be absorbed by patients with CKD owing to poor clearance of this ion, which can produce toxic effects including encephalopathy, osteomalacia, proximal myopathy and anaemia. Dialysis dementia was a disease observed among haemodialysis patients associated with aluminium deposition in the brain and exacerbated by aluminium in the water supply and the use of aluminium cooking pans. Desferrioxamine (4–6 g in 500 mL of saline 0.9% per week) has been used to treat this condition by removing aluminium from tissues by chelation. The tendency of aluminium to cause constipation is an added disadvantage. Therefore, aluminium as a phosphate binder in CKD should be used with caution.

Vitamin D deficiency and hyperparathyroidism

Vitamin D deficiency may be treated with the synthetic vitamin D analogues 1α-hydroxycholecalciferol (alfacalcidol) at 0.25–1 μcg/day or 1,25-dihydroxycholecalciferol (calcitriol) at 1–2 μcg/day. The serum calcium level should be monitored, and the dose of alfacalcidol or calcitriol adjusted accordingly. Hyperphosphataemia should be controlled before starting vitamin D therapy since the resulting increase in the serum calcium concentration may result in soft tissue calcification.

A new agent, paricalcitol, has recently been suggested for use in patients who either do not respond to alfacalcidol or who need doses of alfacalcidol that are impractical because of hypercalcaemia. Paricalcitol is a synthetic, biologically active vitamin D analogue that selectively upregulates the vitamin D receptor in the parathyroid glands reducing PTH synthesis and secretion. It also upregulates the calcium sensing receptor in the parathyroids and reduces PTH by inhibiting parathyroid proliferation, PTH synthesis and secretion without affecting calcium or phosphorus levels.

The rise in 1,25-dihydroxycholecalciferol and calcium levels that result from starting vitamin D therapy usually suppresses the production of PTH by the parathyroids. If vitamin D therapy does not correct PTH levels then parathyroidectomy, to remove part or most of the parathyroid glands, may be needed. This surgical procedure was once commonly performed on CKD patients, but is now less frequent owing to effective vitamin D supplementation.

Cinacalcet is a calcimimetic which increases the sensitivity of calcium sensing receptors to extracellular calcium ion, this results in reduced PTH production. The benefit of this treatment is the suppression of PTH without resultant hypercalcaemia. It is recommended (NICE, 2007) for use as an alternative to parathyroidectomy for patients who are not fit enough to undergo this procedure. Common therapeutic problems in chronic renal failure are summarised in Table 18.4.

Renal transplantation

Renal transplantation has transformed the outlook for many patients with end stage renal disease. The clinical outcomes of renal transplantation are now excellent. One-year patient and graft survival is 98% and 90–95%, respectively, and most patients who receive a transplant will never need to return to dialysis treatment. A renal transplant performed today in the developed world will continue to function, on average, in excess of 15 years. However, an important consideration is that renal transplantation is the treatment of choice for patients with end stage renal disease who are fit to receive a renal transplant; this recognises that many patients in end stage renal disease are frail and elderly and/or have a number of co-existing medical problems such that they are not fit to undergo a major operation (implantation of the kidney) or to tolerate the immunosuppressive drugs that are required to prevent the transplant rejecting. This means that at any given time the majority of patients are not actually on a national waiting list for a renal transplant.

For those patients who are fit enough to receive a renal transplant and are successfully transplanted, there is a profound survival benefit compared to remaining on dialysis treatment. The average transplant recipient lives two or three times as long as a matched dialysis patients who does not receive a renal transplant but remains on dialysis treatment. In addition, a transplant patient is less likely to be hospitalised and has a better quality of life than a dialysis patient. The secondary complications of CKD such as anaemia and bone disease resolve in many patients who are successfully transplanted. Furthermore, there are major health economic benefits to renal transplantation compared to dialysis. Transplantation is a far less expensive treatment than dialysis, particularly after the first year, when the large majority of the costs are limited to payment for the immunosuppressive drugs.

One of the major challenges for renal transplantation is the identification of a sufficient number of donor kidneys to fulfil demand. This is reflected in the increasing number

Table 18.4 Common therapeutic problems in chronic renal failure

Problem	Comment
Drug choice	Care with choice/dose of all drugs. Care to avoid renotoxic agents pre-dialysis to preserve function. Beware herbal therapies as some contain immune system boosters (reverse immunosuppressant effects) and some are nephrotoxic
Drug excretion	CKD will lead to accumulation of drugs and their active metabolites if they are normally excreted by the kidney
Dietary restrictions	Restrictions on patient often severe. Fluid allowance includes foods with high water content, for example, gravy, custard, and fruit
Hypertension	Frequently requires complex multiple drug regimens. CCBs can cause oedema that might be confused with fluid overload
Analgesia	Side-effects are increased. Initiate with low doses and gradually increase. Avoid pethidine as metabolites accumulate. Avoid NSAIDs unless specialist advice available
Anaemia	Epoetin requires sufficient iron stores to be effective. Absorption from oral iron supplements may be poor and i.v. iron supplementation might be required. Care required to make sure that epoetin use does not produce hypertension
Immunosuppression	Use of live vaccines should be avoided (BCG, MMR, mumps, oral polio, oral typhoid, smallpox, yellow fever)
Pruritis (itching)	Can be severe. Treat with chlorphenamine; less sedating antihistamines often less effective. Some relief with topical agents, for example, crotamiton
Restless legs	Involuntary jerks can prevent sleep. Clonazepam 0.5–1 mg at night may help

of people who are waiting for a kidney; in the UK the average time on the waiting list before transplantation is around 3 years. Kidneys donated for the national waiting list are harvested from deceased donors. At the time of donation, donors are classified as dead as a consequence of either brain stem or cardiac death; these are also called heart beating and non-heart beating donors, respectively.

The numbers of deceased donors as a proportion of those on the waiting list for a kidney transplant have fallen. Therefore, living donor transplantation has become increasingly common. In addition to part addressing the scarcity of donor organs, patients who receive kidney transplants from living donors have better outcomes than patients who receive deceased donor kidneys. This is due to a number of factors, including the quality of the organs, because living donors undergo a detailed health screening and if there is any indication that they have significant medical problems they are excluded from donation.

One of the major factors responsible for excellent outcomes for kidney transplant recipients is the use of immunosuppressive drugs to control the response the immune system of the recipient mounts against the donor kidney. This is called an alloresponse. Alloimmunity refers to an immune response against tissue derived from an individual of the same species as the recipient of the tissue.

The major disadvantage of all immunosuppressive agents is their relative non-specificity, in that they cause a general depression of the immune system. This exposes the patient to an increased risk of malignancy and infection, which is an important cause of morbidity and mortality.

Immunosuppressants

The major pharmacological groups of immunosuppressive agents are summarised in Table 18.5.

Transplant recipients receive a high load of immunosuppression at the time of transplantation; this is known as induction immunosuppression. Induction immunosuppression is to protect the transplant from the high immunological risk that is present in the first few weeks after surgery. In the months following the transplant, the immunosuppression load is then incrementally reduced. Most patients will reach long-term low dose maintenance immunosuppression sometime between 6 and 12 months after the transplant. However, whilst the transplant remains in the recipient it continues to represent an immunological risk; whilst overt,

Table 18.5 Mechanism of action of immunosuppressants commonly used following renal transplantation

Drug	Mechanism	Comment
Steroids	Bind to steroid receptors and inhibit gene transcription and function of T-cells, macrophages and neutrophils	Prophylaxis against and reversal of rejection
Ciclosporin	Forms complex with intracellular protein cyclophilin → inhibits calcineurin. Ultimately inhibits interleukin-2 synthesis and T-cell activation	Long-term maintenance therapy against rejection
Tacrolimus	Forms complex with an intracellular protein → inhibits calcineurin	Long-term maintenance therapy against rejection Rescue therapy in severe or refractory rejection
Sirolimus	Inhibits interleukin-2 cell signalling → blocks T-cell cycling and inhibits B-cells	Usually used in combination with ciclosporin ± steroids
Mycophenolate	Inhibits inosine monophosphate dehydrogenase → reduces nucleic acid synthesis → inhibits T- and B-cell function	Usually used in combination with ciclosporin/tacrolimus ± steroids
Azathioprine	Incorporated as a purine in DNA → inhibits lymphocyte and neutrophil proliferation	Usually used in combination with ciclosporin/tacrolimus ± steroids
Muromonab (OKT3, mouse monoclonal anti-CD3)	Binds to CD3 complex → blocks, inactivates or kills T-cell. Short $t_{1/2}$	Prophylaxis against rejection Reversal of severe rejection
Polyclonal horse/rabbit antithymocyte or antilymphocyte globulin (ATG, ALG)	Antibodies against lymphocyte proteins → alter T- and B-cell activity	Prophylaxis against rejection Reversal of severe rejection
Humanised or chimaeric anti-CD25 (basiliximab and daclizumab)	Monoclonal antibodies that bind CD25 in interleukin-2 complex → prevent T-cell proliferation	Prophylaxis against acute rejection in combination with ciclosporin and steroids

late rejection is uncommon, it can occur at any time if the patient stops taking their immunosuppressants. For a transplant to last many years, sustained day on day adherence with treatment is essential.

The commonest combination used at induction is the calcineurin inhibitor (CNI) tacrolimus, the anti-proliferative agent mycophenolate mofetil (MMF) and corticosteroids. Most patients also receive antibody induction. The antibody that is most commonly used is a monoclonal anti-CD25 antibody for people at low or medium immunological risk and anti-T-cell polyclonal antibodies (thymoglobulin or ATG) for people at high immunological risk. Patients at high immunological risk include: those who have lost a previous transplant because of rejection; the presence of preformed circulating anti-HLA antibodies at the time of transplantation (sensitisation); and major HLA mismatches (particularly at HLA-DR) between donor and recipient. Guidelines for the use of immunosuppressive therapy in kidney transplant patients have been issued (NICE, 2004). More recent international consensus guidelines recommend use of newer agents such as MMF and emphasise the use of tacrolimus (rather than ciclosporin) as the CNI of choice. Tacrolimus is associated with less acute rejection than ciclosporin and may be associated with better graft function at one year and less graft loss (Knoll and Bell, 1999). However, there is no overwhelming evidence as yet that patients who receive tacrolimus as a CNI from induction have a survival benefit compared to patients who receive ciclosporin. It should be noted that generic/proprietary formulations of some drugs (e.g. tacrolimus and ciclosporin) are not interchangeable.

Calcineurin inhibitors (ciclosporin and tacrolimus)

The discovery and development of ciclosporin and latterly tacrolimus has led to a step improvement in one-year renal transplant survival from 50–70% to 85–95%.

In T-cells that have been exposed to T-cell receptor (TCR) ligation (signal 1) and co-stimulation (signal 2), there is activation of intra-cytoplasmic signalling pathways that include mobilisation of a molecule called calcineurin. Calcineurin contributes to the activation of a molecule called nuclear factor of activated T-cells (NFAT). This factor then migrates to the nucleus and initiates transcription of IL-2 and other pro-inflammatory cytokines which are involved in driving an activated T-cell into a proliferative phase, so that it makes multiple copies of itself. Ciclosporin and tacrolimus affect calcineurin through blocking binding proteins (cyclophilin and tacrolimus-binding protein, respectively) that are important for calcineurin activity.

The action of CNIs is partially selective in that they predominantly target T-cells and have no direct effect on B cells; as a consequence, CNIs are associated with infections seen in people with deficiencies in the cellular limb of the immune response. These are predominantly intracellular infections such as viral, fungal, protozoal and mycobacterial infections.

Both ciclosporin and tacrolimus are critical dose drugs. That is, there is a narrow therapeutic window between underdosing and toxicity. Both drugs, therefore, require monitoring by serum levels. Trough levels are usually taken 12 h after the previous dose and immediately before the next dose.

Ciclosporin

Ciclosporin causes a wide range of side effects, including nephrotoxicity, hypertension, fine muscle tremor, gingival hyperplasia, nausea and hirsutism. Hyperkalaemia, hyperuricaemia, hypomagnesaemia and hypercholestraemia may also occur. Nephrotoxicity is a particularly serious side effect and occasionally necessitates the withdrawal of ciclosporin. There is tremendous inter- and intra-patient variation in absorption of ciclosporin. Blood level monitoring is required to achieve maximum protection against rejection and minimise the risk of side effects. The range regarded as acceptable varies between centres, but is commonly around 100–200 ng/mL in the first 6 months after transplantation and 80–150 ng/mL from 6 months onwards.

Ciclosporin interacts with a number of drugs that either lead to a reduction in ciclosporin levels, increase the risk of rejection or cause an elevation in ciclosporin levels leading to increased toxicity. Some drugs enhance the nephrotoxicity of ciclosporin (Box 18.2).

Ciclosporin should not be administered with grapefruit juice, which should also be avoided for at least an hour predose, as this can result in marked increases in blood concentrations. This effect appears to be due to inhibition of enzyme systems in the gut wall resulting in transiently reduced ciclosporin metabolism.

Tacrolimus

Tacrolimus is not chemically related to ciclosporin, but acts by a similar mechanism. The side effect profile is similar to that of ciclosporin with some subtle differences. Disturbances of glucose metabolism leading to impaired glucose tolerance and new onset diabetes after transplantation (NODAT) occurs in around 10–15% of patients who receive tacrolimus, this is twice as common as the incidence seen in patients who receive ciclosporin. In contrast, hirsutism is less of a problem in patients who receive tacrolimus than those who receive ciclosporin. In patients who are commenced on ciclosporin and then develop an episode of acute rejection, conversion to tacrolimus lowers the risk of recurrent rejection. Tacrolimus is an easier drug to use than ciclosporin. Careful monitoring is required with a target level of 8–15 ng/mL in the first weeks following transplantation which is usually decreased in patients who follow an uncomplicated course to 5–8 ng/mL from 6 months.

Box 18.2 Examples of drug interactions involving ciclosporin

- Reduce ciclosporin serum levels (hepatic enzyme inducers): phenytoin, phenobarbital, rifampicin, isoniazid
- Increase ciclosporin serum levels (hepatic enzyme inhibitors): diltiazem, erythromycin, corticosteroids, ketoconazole
- Enhance ciclosporin nephrotoxicity: aminoglycosides, amphotericin, co-trimoxazole, melphalan

Steroids

Prednisolone is the oral agent commonly used for immunosuppression after renal transplantation, while high-dose intravenous methylprednisolone is given as a single dose at induction with further use limited for cases of acute rejection. The maintenance dose of prednisolone to minimise adrenal suppression is around 0.1 mg/kg/day given as a single dose in the morning. The use of steroid therapy often leads to complications, particularly if high doses are given for long periods. In addition to a cushingoid state, the use of steroids may cause gastro-intestinal bleeding, hypertension, dyslipidaemia, diabetes, osteoporosis and mental disturbances. Patients who are temporarily unable to take oral prednisolone should be given an equivalent dose of hydrocortisone intravenously.

In the past decade, there has been an increasing use of steroid avoidance regimens. This term is misleading as patients still receive steroids, but use is restricted to the first week of transplantation. Currently, there is no long-term evidence to show this approach provides equivalence to a continuous steroid dosing regimen, but one-year outcomes are comparable. If steroids are subsequently withdrawn months after the transplant, then outcomes with steroid avoidance regimens are worse.

Azathioprine

Azathioprine is derived from 6-mercaptopurine and is, therefore, an antimetabolite which reduces DNA and RNA synthesis-producing immunosuppression.

Azathioprine is given orally in a dose of up to 2 mg/kg/day. There is no advantage in giving it in divided doses. Since azathioprine interferes with nucleic acid synthesis, it may be mutagenic, and pharmacy and nursing staff should avoid handling the tablets. Azathioprine has a significant drug interaction with allopurinol, causing fatal marrow suppression and this combination should be avoided.

Mycophenolate mofetil (MMF)

MMF is a pro-drug of mycophenolic acid. It inhibits the enzyme inosine monophosphate dehydrogenase needed for guanosine synthesis which leads to reduced B-cell and T-cell proliferation. However, other rapidly dividing cells are less affected, as guanosine is produced in other cells. Consequently, mycophenolate has a more selective mode of action than azathioprine.

The drug is given in combination with tacrolimus at a dose of 1 g twice a day which can subsequently be reduced after 6 weeks to 750 mg twice a day. A dose of 1.5 g twice a day is prescribed when used in combination with ciclosporin because the ciclosporin interferes with enterohepatic recirculation of mycophenolate metabolites with consequent lower exposure at a similar dose.

Compared to azathioprine, MMF reduces the risk of acute rejection episodes and improves long-term graft survival. However, it is a more potent immunosuppressant than azathioprine and is associated with a significant increased risk of opportunistic infections.

Sirolimus (rapamycin)

Sirolimus is a macrolide antibiotic that binds to the FKBP-25 cellular receptor. This complex initiates a sequence that produces modulation of regulatory kinases that ultimately interfere with the proliferative effects of IL-2 on lymphocytes. The progression of T-cells from the G1 to S phase is blocked, so inhibiting cell division and therefore cell proliferation.

Adverse effects include hyperkalemia, hypomagnesemia, hyperlipidemia, hypertriglyceridemia, leukopenia, anemia, imp-aired wound healing, and joint pain. Currently, the role of sirolimus in renal transplantation has not been clearly defined. In combination with CNIs, it produces additive nephrotoxicity; when used with MMF it increases the risk of marrow suppression and mucosal side effects. Most experts currently limit the use of sirolimus to patients who have declining kidney function as a consequence of CNIs, but where graft function is still maintained to a GFR of >40 mL/min without significant proteinuria.

Monoclonal antibodies

The humanised or chimeric anti-CD25 monoclonal antibodies basiliximab and daclizumab are clinically similar and bind to CD25 in the IL-2 complex of activated T-lymphocytes. This renders all T-cells resistant to IL-2 and therefore prevents T-cell proliferation. They are used as prophylaxis against acute rejection in combination with CNIs and steroids (NICE, 2004). Daclizumab is currently not available in the UK.

Polyclonal antibodies

These were the first antibodies used as immunosuppressants and contain antibodies with a number of different antigen-combining sites. Polyclonal antibodies are used peri-operatively as prophylaxis against rejection and in some cases to reverse episodes of severe rejection. The main preparations are antithymocyte globulin (ATG) or antilymphocyte globulin (ALG).

ATG is produced from rabbit or equine serum immunised with human T-cells. It contains antibodies to human T-cells, which on injection will attach to, neutralise and eliminate most T-cells, thereby weakening the immune response. ALG is similar to ATG, is of equine origin, but is not specific to T-cells as it also acts on B-cells.

It is not certain how polyclonal antibodies act to inhibit T-cell mediated immune responses but depletion of circulating T-cells, modulation of cell surface receptor molecules, induction of energy and apoptosis of activated T-cells have all been proposed.

The main drawback to the use of anti-T-cell sera is the relatively high incidence of side effects, notably anaphylactic reactions including hypotension, fever and urticaria. These reactions are more frequently observed with the first dose and may require supportive therapy with steroids and antihistamines. Severe reactions may necessitate stopping treatment. Steroids and antihistamines may be given prophylactically to prevent or minimise allergic reactions. Pyrexia often occurs on the first day of treatment but usually subsides without requiring treatment. Tolerance testing by administration of a test dose is advisable,

particularly in patients such as asthmatics who commonly experience allergic reactions. In the event of adverse reactions, ALG and ATG can be substituted for each other.

Other precautions

Transplant patients are given prophylactic antibiotic therapy for varying periods postoperatively owing to the risks of infection associated with immunosuppression. Treatment with co-trimoxazole to prevent *Pneumocystis carinii*, isoniazid and pyridoxine in high-risk patients to prevent tuberculosis, valganciclovir to prevent cytomegalovirus, and nystatin or amphotericin to prevent oral candidiasis are commonly used. Vaccination with live organisms (e.g. BCG, MMR, oral poliomyelitis, oral typhoid) must be avoided in the immunosuppressed patient.

Implementation of regular dialysis treatment

End stage renal failure is the point at which the patient will die without the institution of renal replacement by dialysis or transplantation.

The principle of dialysis is simple. The patient's blood and a dialysis solution are positioned on opposing sides of a semi-permeable membrane across which exchange of metabolites occurs. The two main types of dialysis used in CKD are haemodialysis and peritoneal dialysis. Neither has been shown to be superior to the other in any particular group of patients and so the personal preference of the patient is important when selecting dialysis modality. Haemodialysis and acute peritoneal dialysis are discussed in Chapter 17.

As patients with end stage renal failure may require dialysis treatment for many years, adaptations to the process of peritoneal dialysis have been made that enable the patient to follow a lifestyle as near normal as possible. Continuous ambulatory peritoneal dialysis (CAPD) involves a flexible non-irritant silicone rubber catheter (Tenckhoff catheter) that is surgically inserted into the abdominal cavity. Dacron cuffs on the body of the catheter become infiltrated with scar tissue during the healing process, causing the catheter to be firmly anchored in place. Such catheters may remain viable for many years. During the dialysis process thereafter, a bag typically containing 2.5 L of warmed dialysate and a drainage bag are connected to the catheter using aseptic techniques. Used dialysate is drained from the abdomen under gravity into the drainage bag, fresh dialysate is run into the peritoneal cavity and the giving set is disconnected. The patient continues his or her activities until the next exchange some hours later. The procedure is repeated regularly so that dialysate is kept in the abdomen 24 h a day. This is usually achieved by repeating the process four times a day with an average dwell time of 6–8 h. A number of different dialysis solutions are available of which the majority are glucose based.

Another form of peritoneal dialysis is known as automated peritoneal dialysis (APD) in which exchanges are carried out overnight while the patient sleeps. Dialysis fluid is exchanged – three to five times over a 10-h period with volumes of 1.5–3 L each time. During the day time the patient usually has a dwell of fluid within the abdominal cavity.

Since peritoneal dialysis is continuous and corrects fluid and electrolyte levels constantly, dietary and fluid restrictions are less stringent. Blood loss is also avoided, making the technique safer in anaemic patients. Unfortunately, peritoneal dialysis is not an efficient process; it only just manages to facilitate excretion of the substances required and, as albumin crosses the peritoneal membrane, up to 10 g of protein a day may be lost in the dialysate. It is also uncomfortable and tiring for the patient, and is contraindicated in patients who have recently undergone abdominal surgery.

Peritonitis is the most frequently encountered complication of peritoneal dialysis. Its diagnosis usually depends on a combination of abdominal pain, cloudy dialysate or positive microbiological culture. Empirical antibiotic therapy should, therefore, be commenced as soon as peritonitis is clinically diagnosed. Gram-positive cocci (particularly *Staphylococcus aureus*) and Enterobacteriaceae are the causative organisms in the majority of cases, while infection with Gram-negative species and *Pseudomonas* species are well recognised. Fungal infections are also seen, albeit less commonly.

Most centres have their own local protocol for antibiotic treatment of peritonitis. In one example, levofloxacin, a quinolone with good Gram-negative activity is given orally, in combination with vancomycin, which has excellent activity against Gram-positive bacteria, is administered via the intraperitoneal route. As in all situations, the antibiotic regimen should be adjusted appropriately after the results of microbiological culture and sensitivity have been obtained.

Haemodialysis is particularly suitable for patients producing large amounts of metabolites, such as those with high nutritional demands or a large muscle mass, where these substances are produced faster than peritoneal dialysis can remove them. It also provides a back-up for those patients in whom peritoneal dialysis has failed.

The various techniques of haemofiltration, a technique related to haemodialysis, are also discussed in detail in Chapter 17.

Case studies

Case 18.1

Mr D, a 19-year-old undergraduate student, visited his university health centre complaining of a 3-month history of fatigue, weakness, nausea and vomiting that he had attributed to 'examination stress'. His previous medical history indicated an ongoing history of bed wetting from an early age. Laboratory results from a routine blood screen showed the following:

		Reference range
Sodium	137 mmol/L	(135–145)
Potassium	4.8 mmol/L	(3.5–5.0)
Phosphate	2.5 mmol/L	(0.9–1.5)
Calcium	1.6 mmol/L	(2.20–2.55)
Urea	52 mmol/L	(3.0–6.5)
Creatinine	620 µmol/L	(50–120)
Haemoglobin	7.5 g/dL	(13.5–18.0)

Subsequent referral to a specialist hospital centre established a diagnosis of chronic renal failure secondary to reflux nephropathy.

Question

Explain the signs and symptoms experienced by Mr D and the likely course of his disease?

Answer

Mr D is suffering from the signs and symptoms of uraemia resulting from chronic renal failure. Mechanical reflux damage to his kidneys has compromised renal function and resulted in an accumulation of toxins, including urea and creatinine that, in turn, have contributed to his nausea, vomiting and general malaise. His biochemical results indicate other features typical of uraemic syndrome associated with chronic renal failure. The low haemoglobin is indicative of reduced erythropoetin production following progressive kidney damage. Renal osteodystrophy is also present, as inadequate vitamin D production and the raised serum phosphate have contributed to the hypocalaemia.

This patient is likely to have remained symptom free for a period of years despite progressively worsening renal function. The kidneys operate with a substantial functional reserve under normal conditions. Patients generally remain asymptomatic as their renal reserve diminishes. Eventually there is a failure in the ability of the damaged kidney to compensate and symptoms appear late in the condition.

Case 18.2

Mr K, a 43-year-old male with established CKD, had been maintained for 3 years on continuous ambulatory peritoneal dialysis. He was admitted to hospital for cadaveric renal transplantation. On examination he was found to have slight ankle oedema. He weighed 60 kg and his blood pressure was 135/90 mmHg and pulse rate 77 min^{-1}. He was administered the following immunosuppressants preoperatively: an anti-CD25 antibody, tacrolimus, mycophenolate and prednisolone.

Question

How should the immunosuppressants be administered to Mr K and how should immunosuppression be managed postoperatively?

Answer

Anti-CD25 antibodies and high-dose methylprednisolone are given intravenously at the time of the operation. Typically, tacrolimus at 200–300 µcg/kg/day as two split doses, it is important to note that there are two preparations of tacrolimus, a once daily dose and a divided dose preparation. The once daily preparation is called Advagraf® and the twice daily preparation is Prograf®, the preparations are not interchangeable and as a result they must be prescribed by brand name, changes between preparations must only be made by a transplant specialist. MMF at 1 g twice a day and prednisolone at 10 mg twice a day are given as oral doses to continue in the days and weeks following transplantation. These are commenced within 12 h of the operation. In living kidney donation where the transplant operation is planned, patients are preloaded for several days before the transplant. Intravenous tacrolimus is available, but should only be used in exceptional circumstances, usually when the gut is not working and all drugs and nutrition need to be given by the parenteral route.

Early dose adjustments in tacrolimus following transplantation are common and directed by drug levels. These are checked daily for the first week following transplantation; by 6 months they will be checked on alternate weeks. In the long-term, the median dose of tacrolimus is around 2 mg twice a day and the dose of MMF can be reduced to 500–750 mg twice a day in the large majority of patients. The dose of prednisolone is titrated down so that by 3 months it is 5–10 mg/day. Acute rejection episodes, diagnosed on a renal biopsy performed for a decline in graft function are treated with high-dose steroids. For antibody mediated (severe) rejection, plasma exchange and intravenous immunoglobulin are used.

Case 18.3

Mr A is a patient with CKD secondary to chronic interstitial nephritis. He complains of chronic fatigue, lethargy and breathlessness on exertion, palpitations and poor concentration. His recent haematological results were found to be:

		Reference range
Haemoglobin	**5.6 g/dL**	**(13.5–17.5)**
Red cell count	**2.92 × 10^9 L^{-1}**	**(4.5–6.5 × 10^9 L^{-1})**
Haematocrit	**0.208**	**(0.40–0.54)**
Serum ferritin	**88.0 µcg/L**	**(15–300)**

Question

Explain Mr A's symptoms and haematological results and outline the optimal treatment.

Answer

Mr A's symptoms are most likely to result from a normochromic, normocytic anaemia caused by renal failure. Levels of erythropoetin produced by the kidney are reduced in renal failure. Production of erythropoetin from extrarenal sites, for example, liver, are not sufficient to maintain erythropoesis, which is also inhibited by uraemic toxins and hyperparathyroidism. The anaemia associated with renal failure is further compounded by a reduction in red cell survival through low-grade haemolysis, bleeding from the gastro-intestinal tract and blood loss through dialysis, aluminum toxicity which interferes with haem synthesis, and iron deficiency, usually through poor dietary intake.

Therapy with epoetin is the treatment of choice. However, iron and folate deficiencies should be corrected if epoetin therapy is to be successful. Iron demands are generally raised during epoetin treatment and iron status should be regularly monitored. If serum ferritin falls below 100 µcg/L then iron supplementation should be started. Often intravenous iron is required to provide an adequate supply, despite the dangers associated with administration of iron by this route.

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19 Hypertension

A. G. Dyker

Key points

- Hypertension can be defined as a condition in which blood pressure is elevated to an extent where benefit is obtained from blood pressure lowering. There is no clear-cut blood pressure threshold separating normal from hypertensive individuals. The risk of complications is related to the levels that blood pressure is elevated.
- The World Health Organization has identified hypertension as one of the most important preventable causes of premature morbidity and mortality.
- Hypertension should not be seen as a risk factor in isolation and decisions on management should not focus on blood pressure alone but on total cardiovascular risk.
- The complications of hypertension include stroke, myocardial infarction, heart failure, renal failure and dissecting aortic aneurysm.
- Modest reductions in blood pressure result in substantial reductions in the relative risks of these complications.
- For correct diagnosis, careful measurement of blood pressure is necessary on several occasions using well-maintained and validated equipment.
- Non-pharmacological interventions are important and include weight reduction, avoidance of excessive salt and alcohol, increased intake of fruit and vegetables and regular aerobic exercise. Other cardiovascular risk factors such as smoking, dyslipidaemia and diabetes should be addressed.
- A large selection of antihypertensive drugs is available. It is important to use drugs that minimise patient side effects.
- The most appropriate choice of initial drug therapy depends on the age and racial origin of the patient, as well as the presence of other medical conditions. For younger white patients, an ACE inhibitor is recommended as first-line treatment. For older patients and black people, a calcium channel blocker or thiazide diuretic is an appropriate initial choice.
- Many people need combinations of drugs to achieve adequate blood pressure control. Medication should be convenient to take and adverse effects should be avoided.

Hypertension (high blood pressure) is an important risk factor for the future development of cardiovascular disease. It can be defined as a condition where blood pressure is elevated to an extent that clinical benefit is obtained from blood pressure lowering. Blood pressure measurement includes systolic and diastolic components, and both are important in determining an individual's cardiovascular risk.

Blood pressure is continuously distributed in the population and there is no clear cut-off point between hypertensive and normotensive subjects, although a figure of systolic/diastolic blood pressure of 140/90 mmHg is considered the upper limit of 'normal'. Such values that are used as treatment thresholds or targets are, however, largely arbitrary. Treatment decisions in milder hypertensive subjects should now be made on the basis of patients' overall future risk of vascular disease. There is, however, considerable evidence from clinical trials to demonstrate that treatment of subjects with blood pressures above the threshold currently used in clinical practice results in important clinical benefits. Hypertension is largely a condition of older individuals. While diastolic pressure peaks at age 50, systolic pressure continues to increase with advancing age, making isolated systolic hypertension a common feature of old age. Generally, the risk of cardiovascular disease doubles for every 20/10 mmHg rise in blood pressure.

The cardiovascular complications associated with hypertension are shown in Box 19.1. The most common and important of these are stroke and myocardial infarction. An increase of 5 mmHg in usual diastolic blood pressure is associated with a 35–40% increased risk of stroke. There is a similar but less steep association for coronary heart disease risk. The risk of heart failure is increased six-fold in hypertensive subjects. Meta-analysis of clinical trials has indicated that these risks are reversible with relatively modest reductions in blood pressure of 10/6 mmHg associated with a 38% reduction in stroke and 16% reduction in coronary events (Collins et al., 1990), while a 5 mmHg reduction in blood pressure is associated with a 25% reduction in risk of renal failure.

The absolute benefits of blood pressure lowering achieved as a result of these relative risk reductions depend on the underlying level of risk in an individual. High-risk subjects

Box 19.1 Complications of hypertension

- Myocardial infarction
- Stroke
  - Cerebral/brainstem infarction
  - Cerebral haemorrhage
  - Lacunar syndromes
  - Multi-infarct disease
- Hypertensive encephalopathy/malignant hypertension
- Dissecting aortic aneurysm
- Hypertensive nephrosclerosis
- Peripheral vascular disease

gain more benefit in terms of events saved per year of therapy. Absolute risk is highest in those who already have evidence of cardiovascular disease, such as previous myocardial infarction, transient ischaemic attack or stroke, or who have other evidence of cardiovascular dysfunction such as electrocardiogram (ECG) or echocardiograph abnormality. Risk is also increased in the elderly and in people with diabetes or renal failure and is further enhanced by other risk factors such as smoking, dyslipidaemia, obesity and sedentary lifestyle. In those under the age of 75, men are at greater risk than women. Cardiovascular risk in an individual who has no current cardiovascular disease can be estimated from coronary risk prediction charts (Joint British Societies, 2005; see Chapter 24).

Epidemiology

Between 10% and 25% of the population are expected to benefit from drug treatment of hypertension; the exact figure depending on the cut-off value for blood pressure and the age group considered for active treatment.

In 90–95% of cases of hypertension, there is no underlying medical illness to cause high blood pressure. This is termed 'essential' hypertension, so named because at one time it was erroneously believed to be an 'essential' compensation mechanism to maintain adequate circulation. The precise aetiology of essential hypertension is currently unknown. Genetic factors clearly play a part as the condition clusters in families, with hypertension being twice as common in subjects who have a hypertensive parent. Genetic factors account for about one-third of the blood pressure variation between individuals, although no single gene appears to be responsible except in some rare conditions such as polycystic kidney disease and other metabolic conditions such as Liddle's syndrome (Beevers et al., 2001). The remaining 5–10% of cases are secondary to some other disease process (Box 19.2).

Box 19.2 Causes of hypertension

Primary hypertension (90–95%)
- Essential hypertension

Secondary hypertension (5–10%)
- Renal diseases
- Endocrine diseases
  - *Steroid excess*: hyperaldosteronism (Conn's syndrome); hyperglucocorticoidism (Cushing's syndrome)
  - *Growth hormone excess*: acromegaly
  - *Catecholamine excess*: phaeochromocytoma
  - *Others*: pre-eclampsia
- Vascular causes
  - *Renal artery stenosis*: fibromuscular hyperplasia; renal artery atheroma; coarctation of the aorta
- Drugs
  - Sympathomimetic amines
  - Oestrogens (e.g. combined oral contraceptive pills)
  - Ciclosporin
  - Erythropoietin
  - NSAIDs
  - Steroids

Hypertension is more common in black people of African Caribbean origin, who are also at particular risk of stroke and renal failure. Hypertension is exacerbated by other factors, for example, high salt or alcohol intake or obesity.

Regulation of blood pressure

The mean blood pressure is the product of cardiac output and total peripheral resistance. In most hypertensive individuals, cardiac output is not increased and high blood pressure arises as a result of increased total peripheral resistance caused by constriction of small arterioles.

Control of blood pressure is important in evolutionary terms and a number of homeostatic reflexes have evolved to provide blood pressure homeostasis. Minute-to-minute changes in blood pressure are regulated by the baroreceptor reflex, while the renin–angiotensin–aldosterone system is important for longer term salt, water and blood pressure control. Long-term increases in shear stress can cause vascular remodelling of the endothelium which lead to the formation of a procoagulant rather than anticoagulant surface. At the same time, systems that lead to vascular relaxation, for example nitric oxide, are overcome by increased sensitivity to vasoconstricter substances such as endothelin which predispose to vascular disease and further increases in peripheral resistance which lead to a vicious cycle increasing blood pressure further due to the increase in vascular resistance. Other substances with a role in controlling blood pressure include atrial natriuretic peptide, bradykinin and antidiuretic hormone. Some new therapies seek to treat high blood pressure by modifying responses to these substances, for example, the endothelin antagonist darusentan.

Clinical presentation

Hypertension is often an incidental finding when subjects present for screening or with unrelated conditions. Severe cases may present with headache, visual disturbances or evidence of target organ damage (stroke, ischaemic heart disease or renal failure). In the UK, all patients under 80 years of age should have their blood pressure checked at least every 5 years, with an annual review for those with high normal values in the range 135–139 mmHg systolic or 85–89 mmHg diastolic.

Malignant (accelerated) hypertension

Malignant or accelerated hypertension is an uncommon condition characterised by greatly elevated blood pressure (usually >220/120 mmHg) associated with evidence of ongoing small vessel damage. Fundoscopy may reveal papilloedema, haemorrhages and/or exudates, while renal damage can manifest as haematuria, proteinuria and impaired renal function. The condition may be associated with hypertensive encephalopathy, which is caused by small vessel changes in the cerebral circulation associated with cerebral oedema. The clinical features are confusion, headache, visual loss, seizures and coma. Brain imaging (particularly MRI) usually demonstrates extensive

white matter changes. Malignant hypertension is a medical emergency that requires hospital admission and rapid control of blood pressure over 12–24 h towards normal levels.

Management of hypertension

In the UK, the management of hypertension is guided by consensus guidelines produced by the British Hypertension Society (BHS) and the National Institute for Health and Clinical Excellence (NICE). In 2004, there were significant differences between NICE and BHS guidance but these were addressed in the form of modified joint guidance issued in 2006 which specifically addressed the areas of controversy (National Collaborating Centre for Chronic Conditions: Hypertension, 2006). The European Society of Hypertension also published a task force discussion document in January 2009 and formal guidance in 2007 (Mancia et al., 2009).

Diagnosis of hypertension

In the UK, it is recommended that all adults have their blood pressure measured every 5 years. Those with high normal (130–139 mmHg systolic or 85–89 mmHg diastolic) or previous high readings should have annual measurement.

Blood pressure should be measured using a well-maintained sphygmomanometer of validated accuracy. Blood pressure should initially be measured in both arms and the arm with the highest value used for subsequent readings. The subject should be relaxed and, at least at the first presentation, blood pressure should be measured in both the sitting and the standing positions. An appropriate sized cuff should be used since one that is too small will result in an overestimation of the patient's blood pressure. The arm should be supported level with the heart and it is important that the patient does not hold their arm out since isometric exercise increases blood pressure. Blood pressure is measured using the Korotkov sounds which appear (the first phase) and disappear (the fifth phase) over the brachial artery as pressure in the cuff is released. Cuff deflation should occur at approximately 2 mmHg/s to allow accurate measurement of the systolic and diastolic blood pressures. The fourth Korotkov phase (muffling of sound) has previously been used for diastolic blood pressure measurement but is not currently recommended unless Korotkov V cannot be defined. Having established that the blood pressure is increased, the measurement should be repeated several times over several weeks, unless the initial measurement is at dangerously high levels, in which case several measurements should be made during the same clinic attendance.

Home or ambulatory blood pressure measurements

Some people develop excessive and unrepresentative blood pressure rises when attending the doctor's surgery, so-called 'white coat' hypertension. These patients can be diagnosed if they use a blood pressure machine themselves at home or by 24-h ambulatory blood pressure monitoring. Home blood pressure measurement is inexpensive but it is important to have a machine of validated accuracy that the patient can use properly. Ambulatory blood pressure monitoring over 24 h is also useful for patients who have unusual variability in blood pressure, resistant hypertension or symptoms suggesting hypotension. Home or ambulatory blood pressure measurements are usually lower than clinic recordings, on average by 12/7 mmHg.

Assessment of the hypertensive patient

Secondary causes

It is important to take a careful history checking for features that might suggest a possible secondary cause of hypertension. Examples would be symptoms of renal disease, for example, haematuria, polyuria, etc., or the paroxysmal symptoms that suggest the rare diagnosis of phaeochromocytoma and include headache, postural dizziness, syncope. A careful physical examination should be performed for abdominal bruits, which suggest possible renal artery stenosis, radiofemoral delay which suggest coarctation of the aorta and palpable kidneys which suggest polycysctic kidney disease. Laboratory analysis should include a full blood count, electrolytes, urea, creatinine and urinalysis. In some patients, further investigations may be appropriate, for example, ultrasound of the abdomen or isotope renogram where renal disease is suspected. A renin–angiotensin ratio is a useful screening test to investigate for possible hyperaldosteronism while serum metanephrine and urinary catecholamines may detect underlying phaeochromocytoma.

A low serum potassium may alert to the presence of hyperaldosteronism but it should be remembered that renin levels are suppressed by β-blockers and aldosterone by angiotensin converting enzyme inhibitors and receptor antagonists. A very high aldosterone/renin ratio may suggest Conn's syndrome or primary hyperaldosteronism. This is usually caused by a benign adenoma or simple hyperplasia within the zona glomerulosa of the adrenal gland, the presence of which may be demonstrated by CT or MRI scanning. The tumours may be surgically resected, but where there is a suggestion of hyperaldosteronism and no obvious tumour on imaging, patients may still respond to spironolactone, an aldosterone antagonist, while remaining relatively resistant to other antihypertensives.

Contributing factors

The patient should also be assessed for possible contributory factors to hypertension such as obesity, excess alcohol or salt intake and lack of exercise. Occasionally, hypertension may be provoked by the use of drugs (see Box 19.2), including over-the-counter medicines used as cold and flu remedies. Other risk factors should also be documented and addressed, for example, smoking, diabetes and hyperlipidaemia. It is important to establish whether there is a family history of cardiovascular disease.

Evidence of end-organ damage

The patient should also be examined carefully for evidence of end-organ damage from hypertension. This should include examination of the optic fundi to detect retinal changes.

An ECG should be performed to detect left ventricular hypertrophy or subclinical ischaemic heart disease. It is advisable to check the renal function and test the urine for signs of microalbuminutria which may be an indicator of a higher risk of future end-stage renal disease and overall vascular risk.

Determination of cardiovascular risk

An accurate assessment of cardiovascular disease risk is essential before recommending appropriate management in hypertension. Patients with documented atheromatous vascular disease, for example, previous myocardial infarction or stroke, angina or peripheral vascular disease are at high risk of recurrent events. Those with type 2 diabetes over 40 years of age are also at high risk and can be regarded as 'coronary equivalents', that is, with risks similar to non-diabetic patients with previous myocardial infarction. For non-diabetic patients without vascular disease it is necessary to estimate cardiovascular risk (see Chapter 24). A 10-year cardiovascular disease risk of 20% (equivalent to a 15% coronary heart disease risk) is regarded as an appropriate threshold for antihypertensive therapy in patients with moderate hypertension, as well as for lipid-lowering therapy. Treatment decisions based on these tables will favour treatment in elderly subjects. While a younger patient may be at lower absolute risk over 10 years and may not meet the criteria for blood pressure and lipid treatment, they may be at higher lifetime and longer term risk of premature death and vascular disease and, thus, still merit risk factor intervention.

Other factors to consider include microalbuminuria which increases cardiovascular risk by a factor of 2–3 and the combination of reduced GFR and microalbuminuria may increase risk by as much as six-fold (Cirillo et al 2008; Sehestedt et al., 2009).

Treatment

Non-pharmacological approaches

Non-pharmacological management of hypertension is important, although the effects are often disappointing. Patients with mild hypertension in the range 140–159/90–100 mmHg can be assessed for levels of risk while offered lifestyle advice. General health education is important to allow patients to make informed choices about management. In order to maximise potential benefit, patients should receive clear and unambiguous advice, including written information they can digest in their own time. Written advice for patients can be downloaded from the BHS website (http://www.bhsoc.org/).

In patients who are overweight, weight loss results in reduction in blood pressure of about 2.5/1.5 mmHg/kg. The DASH diet (Dietary Approaches to Stop Hypertension) was evaluated in a clinical trial and found to lower blood pressure significantly (4.5/2.7 mmHg) compared with a typical US diet. This diet emphasises fruit, vegetables, and low-fat dairy produce in addition to fish, low-fat poultry and whole grains while minimising red meat, confectionary and sweetened drinks (Appel et al., 1997). Subjects should reduce their salt intake, for example, by not adding salt to food on the plate. A daily sodium intake of <100 mmol (i.e. 6 g sodium chloride or 2.4 g elemental sodium) should be the aim. There is a significant amount of hidden salt in processed meat, ready meals, cheese and even bread. A dietary assessment may be required to accurately quantify a patient's salt intake and advise on how reductions might be made.

Most subjects will need to control their intake of calories and saturated fat. Regular aerobic exercise, at a level appropriate to the individual subject, at least 3 times a week for at least 30 min derives maximum benefit. This results in improved physical fitness as well as a reduction in blood pressure. Alcohol intake should be restricted to two (females) or three (males) units per day. Although smoking does not affect blood pressure, it increases cardiovascular risk and patients should quit or, if this is not possible, reduce their cigarette consumption.

Unless hypertension is severe, it is appropriate to observe the subject over several months while instituting non-pharmacological interventions. However, if there is a more urgent need for drug treatment, non-pharmacological interventions should occur in parallel.

Drug treatment

Treatment thresholds

Treatment thresholds are summarised in Table 19.1. Lifestyle advice should be provided to all patients with any degree of hypertension. Patients with severe hypertension (>220/120 mmHg confirmed on several readings on the same occasion) should be treated immediately and some guidance suggests that dual therapy should be commenced immediately in patients with blood pressure >20 mmHg above their target as monotherapy is unlikely to be fully effective (Mancia et al., 2007). Patients with blood pressures in the range 160–220/100–120 mmHg should be monitored over several weeks and treated if blood pressure remains in this range. The period of observation before starting treatment depends on the severity of the hypertension and the presence or absence of end-organ damage (see Table 19.1). Patients whose blood pressure is in the range 140–159/90–99 mmHg should be observed annually unless they have evidence of target organ damage, cardiovascular complications, diabetes or a calculated cardiovascular risk >20% over 10 years, in which case drug treatment should be offered. Patients with blood pressure in the range 135–139/85–89 mmHg should be reassessed annually, while those with blood pressure lower than this can be rechecked every 5 years.

Target blood pressures

Within the Hypertension Optimal Treatment (HOT) study (Hansson et al., 1998), patients were allocated diastolic target blood pressures of <90, 85, 80 mmHg. The study struggled to stratify patients effectively into these treatment groups but analysis suggested that the optimum target blood pressure was <140/85 mmHg with little benefit in lowering to lower levels of 120/70 mmHg but also little evidence of harm.

Table 19.1 Threshold blood pressures for intervention

Initial blood pressure		Management
Systolic (mmHg)	Diastolic (mmHg)	
Malignant hypertension		Admit and treat immediately
>220	>120	Repeat several times at the same attendance and treat immediately if blood pressure persists in this range
180–219	110–119	Confirm over 1–2 weeks and treat if blood pressure remains in this range
160–179	100–109	Repeat over 3–4 weeks (end-organ damage present) or 2–12 weeks (no end-organ damage), institute non-pharmacological measures and treat if blood pressure persists in this range
140–159	90–99	Repeat over several weeks. Institute non-pharmacological measures. Treat if remains in this range and patient has target organ damage, cardiovascular complications or an estimated 10-year cardiovascular risk >20%. Otherwise reassess annually
135–139	85–89	Reassess annually
<135	<85	Reassess in 5 years

The UK Prospective Diabetes Study Group (1998a,b) suggested 'tight' blood pressure control was better than less tight in patients with non-insulin-dependent diabetes. The targets in the UK Prospective Diabetes Study were 'tight' <150/85 mmHg and 'less tight' <180/105 mmHg but the actually achieved blood pressures were lower, for example, 154/87 mmHg versus 144/82 mmHg. Recommendations in diabetics have, therefore, suggested treating to a target of 140/80 mmHg or less, although few studies have successfully lowered blood pressure to these levels.

A more recent study (Cardio-Sis) randomised non-diabetic subjects with systolic blood pressure >150 mmHg to target systolic blood pressure of <140 or <130 mmHg (Verdecchia et al., 2009). The primary end-point was left ventricular hypertrophy though the secondary end-point of a composite cardiovascular end-point was reduced (as well as the primary end-point) in the 130-mmHg group, with no increase in adverse events. This, however, is not robust enough evidence to recommend a reduction in blood pressure target levels and would require a larger study of hard clinical end-points to confirm these findings.

Achievement of target blood pressures is incorporated as a quality indicator for the General Medical Services Contract for primary care doctors in the UK. Diabetic patients are an exception and benefit from more aggressive blood pressure reduction. Target blood pressures for diabetic and non-diabetic subjects are summarised in Table 19.2. It should be emphasised that the audit standard will not be achieved in all patients.

Table 19.2 Target clinic blood pressures according to British Hypertension Society guidelines 2004 (Williams et al., 2004)

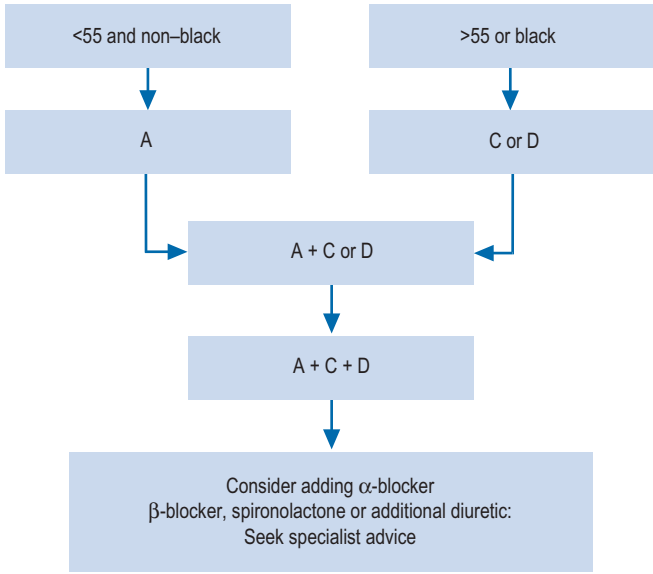
	Clinic blood pressure	
	No diabetes (mmHg)	Diabetes (mmHg)
Optimal treated blood pressure	<140/85	<130/80
Audit standard	<150/90	<140/80

Antihypertensive drug classes

β-Adrenoreceptor antagonists

The mode of action of β-adrenoreceptor antagonists in hypertension is uncertain. β-Adrenoreceptor blockade reduces cardiac output in the short term and during exercise. They also reduce renin secretion by antagonising β-receptors in the juxtaglomerular apparatus. Central actions may also be important for some agents. Non-selective β-blockers may give rise to adverse effects as a result of antagonism of β_2-adrenoceptors, that is, asthma and worsened intermittent claudication. However, the so-called 'cardioselective' (β_1-selective) β-blockers are not entirely free of these adverse effects. Patients who develop very marked bradycardia and tiredness may tolerate a drug with partial agonist activity such as pindolol.

β-Adrenoreceptor antagonists also have substantial clinical trial evidence of benefit over placebo in hypertension, and are relatively inexpensive. However, their use is declining and they have been relegated to fourth-line therapy in the UK according to NICE guidance (Fig. 19.1). This recommendation largely stems from the evidence that they may be less effective at preventing stroke in conjunction with their diabetogenic effects. The Losartan For Endpoint reduction in hypertension (LIFE) study compared an atenolol/thiazide-based regime with a losartan-based regime and demonstrated equivalent levels of blood pressure reduction but with a small excess incidence of stroke in the atenolol arm (Dahlöf et al., 2002). In the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) study, the risk of diabetes was 2.5% higher in the atenolol arm compared with the amlodipine arm with similar increased risk of diabetes found within the atenolol arm of the LIFE study (Dahlöf et al., 2005). A Cochrane review



A = ACE inhibitor; C = calcium channel blocker; D = diuretic

Fig. 19.1 Algorithm for drug sequencing in hypertension.

warned of the excess risk in developing diabetes in patients prescribed combinations of thiazide diuretics and β-blockers. This would equate to one new case per 500 treated (Mason et al., 2004). The combination of thiazide and a β-blocker should, therefore, be avoided if possible, particularly in those who are at risk of developing diabetes (e.g. obese, strong family history of diabetes, South Asian origin).

To complicate matters, however, a long-term 20-year follow-up study of the UKPDS study found similar cardiovascular outcomes between patients on β-blockers and ACE inhibitors with a reduction in all causes of mortality which actually favoured β-blockers (Holman et al., 2008). β-Blockers do remain most suitable for younger hypertensives who have another indication for β-blockade, such as coronary heart disease. β-Blockers are also effective in suppressing atrial fibrillation and this may be one group of patients where first-line therapy with β-blockers is still merited.

It can be safely assumed that the place for β-blockers for patients with hypertension is likely to remain controversial.

Diuretics

There is substantial clinical trial evidence that benefit is obtained from the use of thiazide, for example, bendroflumethiazide, hydrochlorothiazide, or thiazide-like, for example, chlortalidone, indapamide, diuretics in hypertension; these drugs are both inexpensive and well tolerated by most patients. Their diuretic action is achieved by blockade of distal renal tubular sodium reabsorption. Initially, they reduce blood pressure by reducing circulating blood volume but in the longer term they reduce total peripheral resistance, suggesting a direct vasodilatory action.

Although generally well tolerated, thiazide and thiazide-like diuretics may cause hypokalaemia, small increases in LDL-cholesterol and triglyceride, and gout associated with impaired urate excretion. Erectile dysfunction is also common.

Most blood pressure lowering occurs with very low doses of thiazide diuretics. Increasing the dose substantially increases the risk of metabolic disturbance without causing further blood pressure reduction. For bendroflumethiazide it is rarely (if ever) appropriate to use doses greater than 2.5 mg/day and a dose of 1.25 mg daily is often effective. Most studies of diuretics have also incorporated β-blockers and this combination can have adverse metabolic consequences which may lead to new onset diabetes. Within the Anti-hypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), the absolute risk of developing diabetes was 3.5% higher in the chlortalidone group than the lisinopril group (ALLHAT Collaborative Research Group, 2002).

As with the β-blocker saga it remains an issue of contention as to whether this diabetic tendency is clinically significant. There was no reduction in efficacy associated with thiazide use in ALLHAT and indeed there were less heart failure outcomes in the diuretic-treated patients compared with those receiving calcium channel blockers or ACE inhibitors.

Loop diuretics are no more effective at lowering blood pressure than thiazides unless renal function is significantly impaired or the patient is receiving agents that inhibit the renin–angiotensin system. They are also a suitable choice if heart failure is present.

Spironolactone, an aldosterone antagonist, is not suitable for first-line therapy but is an increasingly important treatment option for patients with resistant hypertension. Where hyperaldosteronism is suspected, spironolactone may prove to be effective. Spironolactone is a potassium sparing diuretic and should be used with caution especially if used in combination with ACE inhibitors or angiotensin receptor blockers

(ARBs), and should almost always be avoided with other potassium sparing diuretics, for example, amiloride.

Renin-angiotensin-aldosterone antagonists

ACE inhibitors block the conversion of angiotensin I to angiotensin II, while ARBs block the action of angiotensin II at the angiotensin II type 2_1 receptor. Since angiotensin II is a vasoconstrictor and stimulates the release of aldosterone, antagonism results in vasodilation and potassium retention as well as inhibition of salt and water retention. ACE inhibitors also block kininase production and, thus, prevent the breakdown of bradykinin. This appears to be important in the aetiology of ACE inhibitor induced cough, which is a troublesome side effect in 10–20% of users. ARBs do not inhibit kininase and are an appropriate choice for patients who are intolerant of ACE inhibitors because of cough. ACE inhibitors are also associated with a significant incidence of angioedema, which can in severe cases cause dangerous swelling of the pharyngolargyngeal area leading to stridor, threatening the patient's airway. This adverse reaction is commoner in black subjects.

Calcium channel blockers

These agents block slow calcium channels in the peripheral blood vessels and/or the heart. The dihydropyridine group work almost exclusively on L-type calcium channels in the peripheral arterioles and reduce blood pressure by reducing total peripheral resistance. In contrast, the effect of verapamil and diltiazem are primarily on the heart, reducing heart rate and cardiac output. Long-acting dihydropyridines are preferred because they are more convenient for patients and avoid the large fluctuations in plasma drug concentrations that may be associated with adverse effects.

Although effective for lowering blood pressure and preventing cardiovascular events, adverse effects are common, for example, oedema and flushing. Gum hypertrophy may occur with dihydropyridines and constipation with verapamil. Concerns have previously been raised by observational studies (Psaty et al., 1995) and meta-analysis (Furberg et al., 1995) that there may be an increased risk of coronary heart disease in recipients of dihydropyridine calcium channel blockers. However, randomised clinical trials have not confirmed these observations (Gong et al., 1996, Staessen et al., 1997) and have indicated that dihydropyridines are of similar efficacy to thiazide diuretics in preventing cardiovascular events (Brown et al., 2000).

α-Adrenoreceptor blockers

Drugs of this class antagonise α-adrenoceptors in the blood vessel wall and, thus, prevent noradrenaline (norepinephrine)-induced vasoconstriction. As a result, they reduce total peripheral resistance and blood pressure. Prazosin was originally used but had the disadvantage of being short-acting and causing first-dose hypotension. Newer agents such as doxazosin and terazosin have a longer duration of action. There are concerns about the first-line use of β-blockers since the ALLHAT study has indicated that doxazosin is more often associated with heart failure and stroke than thiazide diuretics (ALLHAT Collaborative Research Group, 2000). However, they are an appropriate choice as add-in therapy for patients inadequately controlled using other agents. They can frequently cause postural hypotension but may alleviate symptoms in men with prostatic hyperterophy.

Centrally acting agents

Methyldopa and moxonidine inhibit sympathetic outflow from the brain, resulting in a reduction in total peripheral resistance. Methyldopa is not widely used because it has pronounced central adverse effects, including tiredness and depression. It continues to be used in pregnancy, since it does not cause fetal abnormalities. It is also occasionally used in patients with resistant hypertension. Moxonidine is a newer agent that blocks central imidazoline and α_2-adrenoceptors found within the medulla oblongata of the brain. It can cause side effects of dry mouth, headache, fatigue and dizziness, although it appears to have fewer central adverse effects than methyldopa. Other centrally acting agents such as clonidine and reserpine are almost never used in modern practice because of their pronounced adverse effects.

Other agents

Several other drugs are available for use for people with more resistant hypertension. Minoxidil is a powerful antihypertensive drug but its use is associated with severe peripheral oedema and reflex tachycardia. It should be restricted to patients with severe hypertension who are also taking β-blockers and diuretics. It causes pronounced hirsutism and is not a suitable treatment for women. Hydralazine can be used as add-on therapy for patients with resistant hypertension but is not well tolerated as it is a profound vasodilator and may occasionally be associated with drug-induced systemic lupus erythematosus. Sodium nitroprusside is a direct-acting arterial and venous dilator that is administered as an intravenous infusion for treating hypertensive emergencies and for the acute control of blood pressure during anaesthesia. Hypertension has previously been treated with ganglion blockers such as guanethidine but these drugs are now of historical interest only.

Recent additions to the licensed armory of antihypertensive agents include the renin antagonist aliskiren. There is evidence that this agent may have a similar blood pressure lowering effect to other agents and may be safely added to other inhibitors of the renin–angiotensin–aldosterone system to provide a greater level of inhibition (O'Brien et al., 2007). Due to its cost and a relative lack of experience in its use, it can only be suggested as an add-on therapy where other more established treatment options have failed to control blood pressure. It is generally well tolerated but may cause diarrhoea at higher doses.

The endothelin antagonist darusentan is undergoing clinical trials in resistant hypertension. Early studies show it may be effective in resistant cases but may be associated with a high incidence of fluid retention (Weber et al., 2009).

Drug selection

Drugs should be chosen on the basis of efficacy, safety, convenience to the patient and cost. For assessing efficacy, it is essential to use evidence from large-scale clinical trials that demonstrate measurable effects on hard end-points like incidence of stroke and other cardiovascular events or death. Smaller scale studies looking at the effects of drugs on blood pressure and surrogate markers such as left ventricular hypertrophy or carotid artery stenosis may generate a hypothesis of a future treatment strategy but should be used to change current strategies. When considering safety, it is important to recognise that these drugs will be taken in the long term and there are advantages to using drugs which have long-established safety records. It is also important to recognise the importance of symptomatic adverse effects since these may reduce adherence. Patients should feel as well during treatment of their blood pressure as they did before drug treatment was instituted. Patient convenience is another important factor and use of once-daily preparations will result in better adherence than more frequent regimens. Since the hypertensive population is very large it is necessary to be conscious of the cost of individual preparations. Combinations of low doses of antihypertensive drugs are often better tolerated than single drugs taken in high dose. The choice of drugs available for treating hypertension is shown in Table 19.3, and common therapeutic problems are noted.

Clinical trial evidence

Initial evidence of benefit in placebo-controlled clinical trials came from studies that primarily involved thiazide diuretics or β-blockers. However, there is increasing evidence of clinical benefit from newer drug classes including ACE inhibitors and calcium channel blockers.

The Blood Pressure Lowering Treatment Trialists Collaboration (2000) carried out a meta-analysis of old against new treatments. They concluded that newer treatments were no more effective than older therapies. Since this study was done several landmark comparative clinical trials have been published.

The Captopril Prevention Project (CAPPP) demonstrated that captopril was as effective as diuretics or β-blockers for preventing cardiovascular morbidity (Hansson et al., 1999a). However, captopril was associated with a 25% higher stroke risk, perhaps because it did not reduce blood pressure as effectively as conventional therapy in this particular study.

The LIFE study demonstrated that losartan was more effective at preventing vascular events, especially stroke, than atenolol in just over 9000 hypertensive patients with left ventricular hypertrophy, although reductions in blood pressure were similar. Losartan was also better tolerated (Dahlöf et al., 2002).

The ALLHAT study (ALLHAT Collaborative Research Group, 2002) involved over 40,000 older, high-risk hypertensive patients with the aim of determining whether the occurrence of fatal coronary heart disease or non-fatal myocardial infarction was lower in those treated with newer agents (amlodipine, lisinopril or doxazosin) compared with a thiazide-like diuretic (chlortalidone). The doxazosin arm was discontinued early because of a higher rate of events, especially heart failure, compared with the diuretic. For the remaining three drugs there was no difference in occurrence of the primary end-point. Chlortalidone was more effective than amlodipine and lisinopril in lowering blood pressure and preventing heart failure and was also marginally more effective than lisinopril in preventing stroke.

The second Australian National Blood Pressure Study Group (Wing et al., 2003) compared enalapril with hydrochlorthiazide in just over 6000 hypertensive subjects recruited in primary care. The primary end-point was any cardiovascular event or death from any cause. In this relatively small study, there was a trend in favour of the ACE inhibitor which was of borderline statistical significance.

The VALUE study (Julius et al., 2004) compared amlodipine and valsartan in high-risk hypertensive subjects. No differences in the primary composite cardiac end-point were observed, although non-fatal myocardial infarction was less common with amlodipine, which also lowered blood pressure to a greater extent. Conversely, onset of diabetes was less common with valsartan.

The ASCOT study (Dahlöf et al., 2005) compared a modern treatment regimen based on amlodipine and perindopril with a traditional regimen based on atenolol and bendroflumethiazide. The study involved over 20,000 high-risk hypertensives. The amlodipine-based therapy was associated with better blood pressure reduction and reductions in the occurrence of cardiovascular events, total mortality and diabetes, although the primary composite end-point was not significantly affected. It is uncertain how much of the benefit can be attributed to the better blood pressure control achieved in the amlodipine-based arm and how specific these findings are to the drug doses and sequencing specified in the trial protocol for each arm of the study.

These various trials have provided results that are conflicting, in part because of differences in trial design and quality. However, there is increasing evidence that β-blockers may be less effective at preventing cardiovascular end-points, as suggested by LIFE and ASCOT studies. In a meta-analysis (Lindholm et al., 2005), β-blockers were less effective than other antihypertensives at preventing stroke, although no significant differences were observed in effects on myocardial infarction or death. There is no consistent evidence that thiazides or thiazide-like drugs are less effective than newer agents in preventing cardiovascular events.

Recommendations for drug sequencing

In the UK, the BHS and NICE issued joint guidelines in 2006 on the order in which drugs should be used (National Collaborating Centre for Chronic Conditions, 2006). This replaced previous guidelines which differed between the two reflecting the ongoing controversy regarding the role of β-blockers. These recommend an initial choice of an

Table 19.3 Summary of antihypertensive drugs and common therapeutic problems

Class	Examples	Major adverse effects	Comment
Diuretics	Thiazides: bendroflumethiazide	Hypokalaemia Gout Glucose intolerance Hyperlipidaemia	Cheap, effective. Efficacy proven in clinical trials Concerns about long-term metabolic effects More appropriate in older patients
	Loops: furosemide	Impotence	Especially for patients with cardiac failure
	K sparing: spironolactone	Uraemia Dehydration Hyperkalaemia Gynaecomastia	Especially for resistant hypertension
β-Blockers	Atenolol Propranolol Metoprolol	Tiredness Reduced exercise tolerance Bradycardia	Cheap Adverse effects common Possibly less effective in preventing cardiovascular events
	Labetalol Celiprolol	Cold peripheries Claudication Wheezing Cardiac failure Impotence	Especially for patients with ischaemic heart disease
Calcium antagonists: dihydropyridine	Nifedipine	Flushing	Not well tolerated (especially early in treatment). Recent trials confirm reductions in stroke and myocardial infarction
	Amlodipine	Oedema Postural hypotension Headache	Similar efficacy to thiazides Especially for elderly patients and those with ischaemic heart disease or diabetes
Calcium antagonists: rate limiting	Verapamil	Bradycardia/heart block	Well tolerated. Suitable for patients with ischaemic heart disease who are unable to tolerate β-blockers
	Diltiazem	Constipation (verapamil only)	Caution needed when used in combination with β-blockers
ACE inhibitors	Captopril Enalapril Lisinopril Perindopril Ramipril	Cough Rash, taste disturbance Renal failure Angioedema	More expensive. Cough very common Appropriate for use in younger patients and those with cardiac failure or diabetes
α-Blockers	Prazosin Doxazosin	Oedema Postural hypotension	More expensive. Adverse effects common. No evidence to date of long-term efficacy. Less effective than thiazides at preventing heart failure and combined cardiovascular outcomes (ALLHAT study)
	Terazosin		Second line
Angiotensin receptor blockers	Losartan Valsartan	Renal failure Oedema	More expensive Especially for patients in whom ACE inhibitor indicated but not tolerated due to cough
	Irbesartan	Headache	More effective in preventing vascular events than atenolol in patients with LVH
Centrally acting vasodilators	Methyldopa	Tiredness	Poorly tolerated. Only used in severe hypertension or hypertension of pregnancy
	Moxonidine	Depression	Third line
Direct-acting vasodilators	Diazoxide Minoxidil Nitroprusside	Oedema Postural hypotension Headache	Poorly tolerated. Only used in severe hypertension

ACE inhibitor or ARB (A) as first-line therapy in younger (<55 years) non-black patients. The rationale for this is that these patients often have hypertension associated with high concentrations of renin. It is, therefore, logical to treat these patients with drugs that antagonise the renin–angiotensin system.

For patients >55 and black patients, who tend to have hypertension associated with low renin concentrations, calcium channel blockers (C) or thiazide diuretics (D) are advocated as first-line options. If initial drug therapy fails to control blood pressure, A and D or C is suggested. Subsequently, a combination of A plus C plus D may be used. After this, further therapies, for example, β-blocker, α-blocker, spironolactone, etc., could be added as necessary to achieve adequate control (Fig. 19.1). β-Blockers may be used in those patients with a high sympathetic drive, in pregnant women where labetolol has a good safety record or where other agents are not tolerated.

European guidance (Box 19.3) has eschewed a formal ranking of treatments and instead suggested a table of drugs and indications where they might be most appropriately indicated (Mancia et al., 2007).

Box 19.3 Conditions favouring use of particular antihypertensive agents (modified from Mancia et al., 2007)

Thiazide diuretics
- Systolic hypertension in the elderly
- Heart failure
- Black patients

ACE inhibitors
- Heart failure
- Left ventricular dysfynction
- Post-myocardial infarction
- Diabetic nephropathy
- Left ventricular hypertrophy
- Proteinuria

β-Blockers
- Angina
- Post-myocardial infarction
- Heart failure (stable)
- Atrial fibrillation
- Pregnancy

Calcium channel blockers (dihydropyridines)
- Systolic hypertension in the elderly
- Angina
- Pregnancy
- Black patients

Calcium channel blockers (verapamil/diltiazem)
- Angina
- Atrial fibrillation

Loop diuretics
- Renal impairment
- Heart failure

Aldosterone antagonists
- Heart failure
- Post-myocardial infarction
- Conn's syndrome

Special patient groups

Race

People of African Caribbean origin have an increased prevalence of hypertension and left ventricular hypertrophy and are at high risk of stroke and renal failure. They obtain particular benefit from reduced salt intake and are also sensitive to diuretic and calcium channel blockers, while β-blockers appear less effective, at least when used as monotherapy. African Caribbean people have reduced plasma renin activity and, as a result, ACE inhibitors and ARBs are also less effective. This was illustrated in the ALLHAT study where stroke and coronary events were more common in black patients randomised to lisinopril compared to those receiving chlortalidone.

British Asians also have an increased prevalence of hypertension, diabetes and insulin resistance and a particularly high risk of coronary heart disease and stroke. There is currently no evidence of a difference in drug response when compared with white Europeans. However, combinations of β-blockers and thiazides should be avoided when possible because of the higher risk of diabetes.

Elderly

The elderly have a high prevalence of hypertension, with over 70% having blood pressures greater than 140/90 mmHg. They are also at high absolute risk of cardiovascular events. Therefore, the absolute benefits of blood pressure treatment are particularly large in this group. Antihypertensive therapy may also reduce the risk of heart failure and dementia. The Study of Cognition and Prognosis in the Elderly (SCOPE) study (Lithell et al., 2003) was designed to investigate the effects of candesartan on the occurrence of cognitive decline or dementia but revealed no benefit, probably because of the lack of difference in blood pressure between the two arms of the study

The elderly are at particular risk of certain adverse effects of treatment such as postural hypotension and it is important that both sitting and standing blood pressure are monitored. Nevertheless, the benefits of therapy are so great that treatment should be offered at any age unless the patient is very frail or their life expectancy is very short. Isolated systolic hypertension (systolic >160 mm Hg, diastolic <90 mmHg) is common in the elderly and there is irrefutable evidence that drug treatment is beneficial in this group (SHEP Co-operative Research Group, 1991, Staessen et al., 1997). The elderly have more variable blood pressure and larger numbers of measurements may be required to confirm hypertension.

Calcium channel blockers and low-dose thiazide diuretics are safe and effective treatments for elderly hypertensive people and their use is endorsed by large-scale clinical trials. β-Blockers are less effective at reducing blood pressure and preventing clinical end-points. The Swedish Trial in Old Patients with hypertension-2 (STOP-2) compared the effects of conventional (β-blocker or thiazide) and newer drugs (ACE inhibitors or calcium channel blockers) on cardiovascular morbidity in older subjects and did not detect significant differences (Hansson et al., 1999b).

In the Hypertension in the Very Elderly Trial (HYVET), 4000 patients with a mean age of 84, blood pressure 160–199 mmHg systolic at entry were treated to a target of systolic 150 mmHg for 1.8 years with indapamide (a thiazide-like diuretic) and if required the ACE inhibitor perindopril. There was a 30% reduction in fatal and non-fatal stroke, 21% reduction in death from all causes, and fewer adverse events in the actively treated group (Beckett, 2008).

The elderly certainly benefit from treatment of hypertension but the threshold and target for treatment has not been fully elucidated. Most studies in the elderly recruited patients with relatively high baseline targets (>160–190 mmHg systolic) achieving blood pressure on treatment of between 150 and 170 mmHg and only one achieved target blood pressure lower than 140 mmHg and in this study outcome was poorer in the treated group (JATOS Study Group, 2008). There may be little benefit in striving for strict systolic targets beyond 150 mmHg in these patients, particularly if control is being achieved to the detriment of overall patient well-being.

Diabetes

In type 1 diabetes, the presence of hypertension often indicates the presence of diabetic nephropathy. In this group, blood pressure reduction and ACE inhibition slow the rate of decline in renal function. To achieve adequate blood pressure control, combinations of drugs will be needed. Thiazides, β-blockers, calcium channel blockers and α-blockers are all suitable as add-on treatments to ACE inhibitors which should be first-line therapy. Target blood pressure should be <130/80 mmHg or <125/75 mmHg if there is diabetic nephropathy. The evidence supporting this recommendation is, however, limited and obtaining such levels of control in diabetics often impossible.

In type 2 (non-insulin dependent) diabetes, hypertension is particularly common, affecting 70% of people in this group. It is strongly associated with obesity and insulin resistance and control of blood pressure is more important for preventing complications than tight glycaemic control. There is no evidence that one group of drugs is more or less effective than any other. The ADVANCE trial treated diabetics with indapamide and perindopril in addition to prestudy antihypertensive agents. The active group was found to have a further reduction in blood pressure and a significant reduction in adverse renal outcomes (21%) (Patel et al., 2007). It remains a subject of debate whether ACE inhibitors and ARBs have specific renoprotective benefits over and above their effects on blood pressure.

Renal disease

In patients with chronic renal impairment, good blood pressure control slows the progression of renal dysfunction. ACE inhibition reduces the incidence of end-stage renal failure but it is not clear if this is a specific effect or non-specific action as a result of blood pressure lowering. ACE inhibitors also reduce 24-h protein loss and should be used in patients with 24-h protein excretion of >3 g or rapidly progressive renal dysfunction. ACE inhibitors may worsen renal impairment in patients with renal vascular disease and careful monitoring of electrolytes and creatinine is mandatory. Salt restriction is particularly important in managing hypertension in renal disease. Thiazide diuretics are ineffective in patients with significant renal dysfunction and loop diuretics should be used when a diuretic is needed.

A further note of caution regarding overtreatment of blood pressure to overaggressive targets comes from the ONTARGET study which randomised patients with vascular disease or high-risk diabetics to high-dose ramipril, telmisartan (ARB) or both. Many patients were already taking polypharmacy for hypertension and blood pressures at entry were approximately 142/82 mmHg in all groups. Treatment reduced blood pressure by 6.4/4.3 mmHg in the ramipril group, 7.4/5.0 mmHg in the telmisartan group and 9.8/6.3 mmHg in the combination group. This would give the combination group a post-treatment blood pressure of 132/76 mmHg. This combination group was associated with adverse renal outcomes, for example, renal failure and high potassium with no improvement in other cardiovascular outcomes (Yusuf et al., 2008a).

Stroke

Hypertension is the most important risk factor for stroke in patients with or without previous stroke. There is increasing evidence that in those with a previous stroke, blood pressure reduction reduces the risk of stroke recurrence as well as other cardiovascular events. The PROGRESS study, while clearly demonstrating a benefit of lowering blood pressure in patients with cerebrovascular disease, only demonstrated benefit in those whose blood pressure was >140 mmHg on entry or who were already on antihypertensives. The size of benefit was proportional to the size of the blood pressure reduction. The combination of perindopril and indapamide lowered systolic blood pressure by 12.3 mmHg and stroke incidence by an impressive 43%, while perindopril alone was associated with a small drop in systolic blood pressure and no reduction in stroke risk (PROGRESS Collaborative Group, 2001). On treatment, blood pressure in the actively treated group was 132 mmHg systolic which has led some to suggest a target of 130 mmHg for such patients but this is based on post hoc analysis and has not been recommended in formal guidance.

The PROFESS study randomised patients with cerebrovascular disease to telmistartan or placebo and obtained systolic blood pressure of 136 in the active group versus 140 mmHg in the placebo group with no difference in the vascular outcomes between the two groups. This may have been due to the relatively small difference in blood pressure between the two groups (Yusuf et al., 2008b).

The question ‘what to do with blood pressure in the setting of acute stroke?’ has remained an evidence-free zone until fairly recently. Blood pressure naturally rises then falls in the days and hours following acute stroke and some have

argued that elevated levels are necessary to maintain brain circulation due to the failure of cerebral autoregulatory mechanisms around the time of stroke. The theory that lowering blood pressure could reduce cerebral perfusion due to a lack of the usual autoregulatory mechanisms is counterweighted by the potential for further damage due to cerebral oedema. The Control Hypertension and Hypotension Immediately Poststroke Study (CHHIPS) randomised acute stroke patients to placebo, lisinopril (sublingual) or intravenous bolus of labetolol and evaluated the incidence of neurological deterioration. There was no adverse outcome in any actively treated group despite reductions in blood pressure (21 vs. 11 mmHg for systolic blood pressure; Potter et al., 2009) This was a relatively small study and larger confirmatory studies are required before firm recommendations for patient management should be made.

In patients with intracerebral haemorrhage, acute reduction of blood pressure has also been demonstrated to be feasible and probably safe with reduced haematoma growth in the actively treated group (Anderson et al., 2008).

Pregnancy

An increased blood pressure before 20 weeks gestation usually indicates pre-existing chronic hypertension that may not have been previously diagnosed. As in all younger hypertensive patients, a careful assessment is needed to exclude possible secondary causes, although radiological and radionuclide investigations should usually be deferred until after pregnancy. Hypertension diagnosed after 20 weeks gestation may also indicate chronic hypertension, which may have been masked during early pregnancy by the fall in blood pressure that occurs at that time. Patients with elevated blood pressure in pregnancy are at increased risk of pre-eclampsia and intrauterine growth retardation. They need frequent checks of their blood pressure, urinalysis and fetal growth. Pre-eclampsia is diagnosed when the blood pressure increases by 30/15 mmHg from measurements obtained in early pregnancy or if the diastolic blood pressure exceeds 110 mmHg and proteinuria is present. There is consensus that blood pressure should be treated with drugs if it exceeds 150–160/100–110 mmHg, although some clinicians use a lower threshold, for example, 140/90 mmHg. Methyldopa is the most suitable drug choice for use in pregnancy because of its long-term safety record. Calcium channel blockers, hydralazine and labetalol are also used. β-Blockers, particularly atenolol, are used less often as they are associated with intrauterine growth retardation. Although diuretics reduce the incidence of pre-eclampsia they are little used in pregnancy because of concerns about decreasing maternal blood volume. ACE inhibitors and ARBs are contraindicated, as they are associated with oligohydramnios, renal failure and intrauterine death.

Meta-analysis of trials suggests that antihypertensive drugs reduce risk of progression to severe hypertension and reduce hospital admissions, although excessive blood pressure reduction may reduce fetal growth.

Oral contraceptives

Use of combined oral contraceptives results, on average, in an increase of 5/3 mmHg in blood pressure. However, severe hypertension can occur in a small proportion of recipients months or years into treatment. Progesterone-only preparations do not cause hypertension so often but are less effective for contraception, especially in younger women. Combined oral contraceptives are not absolutely contraindicated in hypertension unless other risk factors for cardiovascular disease, such as smoking, are present.

Hormone replacement therapy

There is little evidence that hormone replacement therapy is associated with an increase in blood pressure and women with hypertension should not be denied access to these agents if there is an appropriate indication. However, hormone replacement therapy itself does not reduce and may increase the risk of cardiovascular events. Large increases in blood pressure have occasionally been reported in individuals and it is important to monitor blood pressure during the first few weeks of therapy and 6-monthly thereafter. In women with resistant hypertension, during treatment with hormone replacement therapy, the effectiveness of discontinuing hormone replacement should be assessed.

A list of the indications and contraindications to the various antihypertensive agents can be found in Table 19.4.

Ancillary drug treatment

Aspirin

The use of aspirin reduces cardiovascular events at the expense of an increase in gastro-intestinal complications. Its use should be restricted to patients who have no contraindications and either:

- have evidence of established vascular disease or
- have no evident cardiovascular disease but who are over 50 years of age and have either evidence of target organ damage or a 10-year cardiovascular disease risk of >20%.

Blood pressure should be controlled (<150/90 mmHg) before aspirin is instituted.

Lipid-lowering therapy

There is increasing evidence from clinical trials of the benefit of lipid-lowering drug treatment in patients with hypertension. For example, in the ASCOT study lipid-lowering arm (ASCOT-LLA), treatment with atorvastatin 10 mg was associated with substantial reductions in coronary heart disease and stroke, in spite of the fact that those with total cholesterols initially higher than 6.5 mmol/L were excluded from the study (Sever et al., 2003). Lipid-lowering therapy, usually with a statin, should be prescribed to patients under 80 years of age with a total cholesterol >3.5 mmol/L who either have pre-existing vascular disease or a 10-year cardiovascular risk of >20%.

Table 19.4 Use of antihypertensive drugs adapted from British Hypertension Society guidelines

Class	Indications	Contraindications
Diuretics	Elderly ISH Heart failure Secondary stroke prevention	Gout
β-Blockers	Myocardial infarction Angina (Heart failure)	Asthma/chronic obstructive pulmonary disease Heart block (Heart failure) (Dyslipidaemia) (Peripheral vascular disease) (Diabetes, except with coronary heart disease)
Calcium antagonists: dihydropyridine	Elderly isolated systolic hypertension (Elderly) (Angina)	
Calcium antagonists (rate limiting)	Angina (Myocardial infarction)	Combination with β-blocker (Heart block) (Heart failure)
ACE inhibitors	Heart failure Left ventricular (LV) dysfunction Type 1 diabetic nephropathy Secondary stroke prevention (Chronic renal disease) (Type 2 diabetic nephropathy) (Proteinuric renal disease)	Pregnancy Renovascular disease (Renal impairment) (Peripheral vascular disease)
α-Blockers	Benign prostatic hypertrophy (Dyslipidaemia)	Urinary incontinence (Postural hypotension) (Heart failure)
Angiotensin receptor blockers	ACE inhibitor intolerance Type 2 diabetic nephropathy Hypertension with LVH Heart failure in ACE inhibitor-intolerant subjects Post-MI (LV dysfunction post-MI) (Intolerance of other antihypertensive drugs) (Proteinuric renal disease) (Chronic renal failure) (Heart failure)	As ACE inhibitors
Centrally acting vasodilators	Pregnancy (methyldopa only) Resistant hypertension unresponsive to first-line therapy	
Direct-acting vasodilators	Resistant hypertension, unresponsive to first-line therapy	

Note: Strong indications and contraindications are shown. Text in parentheses indicates weak/possible indications or contraindications.

Case studies

Case 19.1

A 55-year-old woman of African Caribbean origin is found to have consistently elevated blood pressure over several weeks, her lowest reading being 155/98 mmHg. She is overweight and has diabetes, and is being treated with metformin. Her renal function and urinalysis are both normal.

Questions

1. Should drug therapy be initiated for her hypertension?
2. If her hypertension was treated with drugs, which agents offer particular advantages, and which should be avoided?

Answers

1. Provided her blood pressure has been measured accurately over several weeks, it should be treated, since her diabetes is an important additional risk factor. It is important to ensure that an appropriately sized blood pressure cuff is being used, in view of her obesity. Non-pharmacological interventions should also take place in parallel. Restriction of salt intake may be particularly helpful in people of African Caribbean race and weight reduction would benefit her hypertension and diabetes.
2. ACE inhibitors are an attractive choice for diabetic patients who have nephropathy. However, there is no evidence of nephropathy in this patient and ACE inhibitors are less effective antihypertensives in people of African Caribbean origin. β-Blockers reduce hypoglycaemic awareness; this is not a contraindication in this case since metformin does not cause hypoglycaemia. However, β-blockers are also less effective in those of African Caribbean descent. Diuretics work well in African Caribbean patients with hypertension, but may worsen glucose tolerance and may not, therefore, be the most appropriate first choice. Calcium channel blockers do not have adverse metabolic effects and are effective in people of this origin and would, therefore, be an appropriate choice. Tight blood pressure control is important and several agents may be required, including diuretics, ACE inhibitors, β-blockers and α-blockers.

Case 19.2

Mr PT, a 35-year-old man, is overweight and has a blood pressure of 178/114 mmHg. He smokes 25 cigarettes daily and drinks 28 units of alcohol per week. He has a sedentary occupation. He eats excessive quantities of saturated fat and salt.

Questions

1. How should this patient be managed?
2. What pharmacological treatment for blood pressure would be appropriate if non-pharmacological treatment was unsuccessful?

   Mr PT subsequently stopped smoking and lost some weight but remained hypertensive. He was treated with atenolol 50 mg daily.

   His blood pressure fell to 136/84 mmHg but he developed tiredness and bradycardia and complained of erectile impotence.
3. What are the treatment options for Mr PT?

Answers

1. Since he is a young man, his absolute risk of cardiovascular events is low, at least for the time being. However, he has several additional risk factors that need to be addressed, including his sedentary lifestyle and his smoking. Non-pharmacological methods have the potential of reducing his blood pressure considerably, including reduction in weight and salt intake. Measurement of plasma cholesterol may help him modify his diet, although he is unlikely to qualify for lipid-lowering therapy in view of his young age.
2. If drug treatment was appropriate, initial treatment with an ACE inhibitor would be consistent with current guidance, in view of his age. This is likely to be more effective for blood pressure lowering than a calcium channel blocker or diuretic. β-Blockers have been recommended as an option in younger patients but are now considered less suitable as initial therapy. Other drugs could be added or substituted if he was intolerant to initial therapy or it did not reduce his blood pressure to target levels.
3. It is possible that he would feel less tired using a β-blocker with intrinsic sympathomimetic activity (e.g. pindolol) but this is by no means guaranteed. The effects on his sexual function are unpredictable. It would probably be better to change him to a drug of a different class such as an ACE inhibitor.
   A calcium channel blocker or thiazide diuretic (although these also commonly cause impotence) may be added if necessary.

Case 19.3

A 24-year-old woman with a family history of hypertension is prescribed an oral contraceptive. Six months after starting this, she is noted to have a blood pressure of 148/96 mmHg.

Question

How should this patient be managed?

Answer

If her blood pressure is consistently raised she may have either essential hypertension or hypertension induced by the oral contraceptive, or a combination. Her blood pressure may fall if her oral contraceptive is discontinued. She will, however, need advice on adequate contraceptive methods. A progesterone-only preparation would be one possibility. She would need careful counselling about the methods available and how successful they are. If her blood pressure remained elevated after discontinuing her oral contraception, she is likely to have underlying hypertension. This may be essential in nature, in view of the family history; however, because of her age she should undergo some investigations to exclude possible secondary causes of hypertension. She is at low risk of complications and there is no urgency to consider drug treatment. If there is a strong wish to use combined oral contraception, it would be important to control other risk factors as far as possible and to consider drug treatment for her hypertension.

Case 19.4

A 73-year-old lady has a long-standing history of hypertension and intolerance to antihypertensive drugs. Bendroflumethiazide was associated with acute attacks of gout, she developed breathlessness and wheezing while taking atenolol, nifedipine caused flushing and headache, and doxazosin was associated with intolerable postural hypotension. Four weeks earlier she had been started on enalapril but was now complaining of a dry persistent cough. Her blood chemistry has remained normal.

Questions

1. Is the patient's cough likely to be an adverse effect of enalapril?
2. What other options are available for controlling her blood pressure?

Answers

1. Yes it is. A dry cough is a common adverse effect of ACE inhibitors. It affects approximately 10–20% of recipients and is more common in women. Some patients are able to tolerate the symptom but in many the drug has to be discontinued.
2. Angiotensin receptor blockers can be used in patients intolerant of ACE inhibitors due to cough. They are unlikely to produce this symptom since they do not inhibit the metabolism of pulmonary bradykinin. Centrally acting agents such as methyldopa or moxonidine could also be considered. However, these are not well tolerated and side effects are quite likely in this patient. A non-dihydropyridine calcium channel blocker such as verapamil is another alternative. Measurement of plasma uric acid could also be considered followed by prophylactic treatment with allopurinol before introducing a diuretic. Alternatively, a trial of spironolactone or the renin antagonist aliskiren could be considered.

Case 19.5

A 23-year-old woman has a normal blood pressure (118/82 mmHg) when reviewed at 8 weeks of pregnancy. In the 24th week of pregnancy, she is reviewed by her midwife and found to have a blood pressure of 148/96 mmHg. Urinalysis is normal.

Questions

1. What is the likely diagnosis?
2. What complications does the patient's high blood pressure place her at increased risk of?
3. Should she receive drug treatment? If so, with which drug? If not, how should she be managed?

Answers

1. She may have gestation-induced hypertension or chronic hypertension that had previously been masked by the fall in blood pressure that happens in early pregnancy.
2. She is at increased risk of pre-eclampsia and intrauterine growth retardation.
3. There are differences of opinion between specialists as to whether blood pressure should be treated at this level during pregnancy. In favour of treatment is the substantial rise over the earlier blood pressure recording. Some specialists would not treat unless the blood pressure was >170/110 mmHg or other complications were present. If she were treated, methyldopa would be a suitable choice. In any event, she needs close monitoring of her blood pressure, urinalysis and fetal growth.

Case 19.6

An elderly patient comes to the pharmacy with a prescription for the following medications: salbutamol inhaler 200 µcg as required, beclometasone inhaler 200 µcg twice daily, bendroflumethiazide 2.5 mg daily, modified release diltiazem 180 mg once daily and atenolol 50 mg daily. The atenolol was being started by the patient's primary care doctor, apparently because of inadequate blood pressure control.

Question

What action should the pharmacist take?

Answer

There are two reasons to be concerned about the addition of atenolol to this patient's drug regimen. First, there is a potentially hazardous interaction with diltiazem which may result in severe bradycardia or heart block. Second, the patient is receiving treatment for obstructive airways disease and this may be worsened by the atenolol. Third, there is increasing evidence to demonstrate the combination of a thiazide and a β-blocker increases the risk of developing diabetes. The prescription should be discussed with the prescriber.

Case 19.7

A patient is admitted to hospital with a stroke. A CT scan of the brain shows a cerebral infarct. The patient's blood pressure is 178/102 mmHg and remains at this level over the first 6 h after admission to the ward.

Question

Should antihypertensive medication be prescribed?

Answer

There is no good evidence that antihypertensive drug treatment is beneficial in the early stages of acute stroke and there is a risk that lowering blood pressure may compromise cerebral perfusion further. However, in the longer term, blood pressure reduction is valuable for preventing further strokes and other cardiovascular events. It would be appropriate to monitor the blood pressure and start treatment after a few days if it remains persistently elevated. A thiazide diuretic and/or ACE inhibitor are commonly used under these circumstances, following the demonstration of benefit in the PROGRESS study (PROGRESS Collaborative Group, 2001).

Case 19.8

A 67-year-old man has been treated for hypertension with atenolol 50 mg daily for several years. He feels well and his blood pressure is controlled. He has read an article in the paper that suggests atenolol is not considered the most suitable drug for treating high blood pressure and enquires about changing his prescription.

Question

Should an alteration to his treatment be recommended?

Answer

There is increasing evidence that β-blockers, including atenolol, may be less effective at preventing cardiovascular events, especially stroke, than other drugs and are associated with a higher risk of development of diabetes, especially if used in combination with thiazide diuretics. They are also less effective at reducing blood pressure in older people. However, if his blood pressure is well controlled and the treatment suits him there is no strong reason to change his medication unless he is at particular risk of diabetes.

Case 19.9

A 58-year-old male patient is noted to have high blood pressure by his primary care doctor. There is no evidence of end-organ damage and he has no other cardiovascular risk factors. The blood pressure remains greater than 160/100 mmHg each time it is checked in the surgery over several weeks, in spite of salt and alcohol reduction. The patient buys a wrist blood pressure monitor in a pharmacy and takes several readings at home. These are all below 130/75 mmHg.

Question

What advice should he be given about the need for drug treatment?

Answer

He may have 'white coat' hypertension. Since this is associated with a lower risk than sustained hypertension he may not need drug treatment. However, before making this judgement it is important to check that his machine is accurate. This can be done by comparing readings with a validated machine, or by checking to see if the make of blood pressure monitor has been verified as accurate by the British Hypertension Study.

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20 Coronary heart disease

D. McRobbie

Key points

- Coronary heart disease (CHD) is common, often fatal and frequently preventable.
- High dietary fat, smoking and sedentary lifestyle are risk factors for CHD and require modification if present.
- Hypertension, hypercholesterolaemia and diabetes mellitus, obesity and personal stress are also risk factors and require optimal management.
- Stable angina should be managed with nitrates for pain relief and β-blockers, unless contraindicated, for long-term prophylaxis. Where β-blockers are inappropriate, the use of calcium channel blockers and/or nitrates may be considered.
- Acute coronary syndromes arise from unstable atheromatous plaques and may be classified as to whether there is ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI).
- ST elevation on the ECG indicates an occluded coronary artery and is used to determine treatment with fibrinolysis or primary angioplasty.
- Patients with NSTEMI may have experienced myocardial damage, are at increased risk of death and may benefit from a glycoprotein IIb/IIIa inhibitor.

Coronary heart disease (CHD), sometimes described as coronary artery disease (CAD) or ischaemic heart disease (IHD), is a condition in which the vascular supply to the heart is impeded by atheroma, thrombosis or spasm of coronary arteries. This may impair the supply of oxygenated blood to cardiac tissue sufficiently to cause myocardial ischaemia which, if severe or prolonged, may cause the death of cardiac muscle cells. Similarities in the development of atheromatous plaques in other vasculature, in particular the carotid arteries, with the resultant cerebral ischaemia has resulted in the term cardiovascular disease (CVD) being adopted to incorporate CHD, cerebrovascular disease and peripheral vascular disease.

Myocardial ischaemia occurs when the oxygen demand exceeds myocardial oxygen supply. The resultant ischaemic myocardium releases adenosine, the main mediator of chest pain, by stimulating the A1 receptors located on the cardiac nerve endings. Myocardial ischaemia may be 'silent' if the duration is of insufficient length, the afferent cardiac nerves are damaged (as with diabetics) or there is inhibition of the pain at the spinal or supraspinal level.

Factors increasing myocardial oxygen demand often precipitate ischaemic episodes and are commonly associated with increased work rate (heart rate) and increased work load (force of contractility). Less commonly, myocardial ischaemia can also arise if oxygen demand is abnormally increased, as may occur in patients with thyrotoxicosis or severe ventricular hypertrophy due to hypertension. Myocardial oxygen supply is dependant on the luminal cross-sectional area of the coronary artery and coronary arteriolar tone. Atheromatous plaques decrease the lumen diameter and, when extensive, reduce the ability of the coronary artery to dilate in response to increased myocardial oxygen demand. Ischaemia may also occur when the oxygen-carrying capacity of blood is impaired, as in iron-deficiency anaemia, or when the circulatory volume is depleted.

CHD kills over 6.5 million people worldwide each year.

Epidemiology

Almost 200,000 people die from CVD in the UK each year with CHD accounting for almost a half of these. About 30% of premature deaths (below 75 years old) in men and 22% of premature deaths in women result from CVD.

The epidemiology of CHD has been studied extensively and risk factors for developing CHD are now well described. Absence of established risk factors does not guarantee freedom from CHD for any individual, and some individuals with several major risk factors seem perversely healthy. Nonetheless, there is evidence that in developed countries, education and publicity about the major risk factors have led to changes in social habits, particularly with respect to a reduction in smoking and fat consumption, and this has contributed to a decrease in the incidence of CHD.

The UK has seen a steady decline in deaths from CHD of about 4.5% per annum since the late 1970s. A recent study indicated that both reductions in major risk factors and improvements in treatment have contributed to this reduction (Unal et al., 2004). While impressive, this rate of decline has not been as great as in other countries like Australia and Finland. In Eastern European countries, the death rates from CHD have increased significantly during the same period.

The improvement in deaths from CHD has been chiefly among those with higher incomes; however, the less prosperous social classes continue to have almost unchanged levels of CHD. Better treatment has also contributed to a decrease

in cardiac mortality, although CHD still accounted for some 94,000 deaths in 2006 in the UK, including 70% of sudden natural deaths, 22% of male deaths and 16% of female deaths. In most developed countries, CHD is the leading cause of adult death but in the UK the poor outcome of lung cancer treatments makes cancer marginally the leading cause. In the UK, in comparison with Caucasians, people of South Asian descent have a 45–50% higher death rate from CHD, and Caribbeans and West Africans have a 35–50% lower rate.

Prevalence

About 3.5% of UK adults have symptomatic CHD. One-third of men aged 50–59 years of age have evidence of CHD, and this proportion increases with age. In the UK, there are about 1.3 million people who have survived a myocardial infarction and about 2 million who have, or have had, angina and this equates to about 5% of men and 3% of women. Approximately 260,000 people suffer a myocardial infarction in any year, of whom 40–50% die.

Mortality increases with age and is probably not due to a particular age-related factor but to the cumulative effect of risk factors that lead to atheroma and thrombosis and hence to CAD. In the USA, age-related death rates for CHD have fallen by 25% over a decade, but the total number of CHD deaths has fallen by only 10% because the population is ageing. Similarly, in the UK the death rates are falling but the numbers living with CHD are increasing.

Women appear less susceptible to CHD than men, although they seem to lose this protection after menopause, presumably because of hormonal changes. Race has not proved to be a clear risk factor since the prevalence of CHD seems to depend much more strongly on location and lifestyle than on ethnic origin or place of birth. It has been shown that lower social or economic class is associated with increased obesity, poor cholesterol indicators, higher blood pressure and higher C-reactive protein (CRP) measurements, an indicator of inflammatory activity.

Risk factors

Traditionally, the main potentially modifiable risk factors for CHD have been considered to be hypertension, cigarette smoking, raised serum cholesterol and diabetes. More recently psychological stress and abdominal obesity have gained increased prominence (Box 20.1). Patients with a combination of all these risk factors are at risk of suffering a myocardial infarction some 500 times greater than individuals without any of the risk factors. Stopping smoking, moderating alcohol intake, regular exercise and consumption of fresh fruit and vegetables were associated independently and additively with reduction in the risk of having a myocardial infarction.

Diabetes mellitus is a positive risk factor for CHD in developed countries with high levels of CHD, but it is not a risk factor in countries with little CHD. Insulin resistance, as defined by high fasting insulin concentrations, is an independent risk factor for CHD in men. In the UK, the mortality rates from CHD are up to five times higher for people with diabetes, while the risk of stroke is up to three times higher.

Box 20.1 Factors that increase or decrease the risk of developing CHD

Factors that increase the risk of CHD
Cigarette smoking
Raised serum cholesterol
Hypertension
Diabetes
Abdominal obesity
Increased personal stress

Factors that decrease the risk of CHD
Regular consumption of fresh fruit and vegetables
Regular exercise
Moderate alcohol consumption
Modification of factors that increase the risk of CHD

While unusual physical exertion is associated with an increased risk of infarction, an active lifestyle that includes regular, moderate exercise is beneficial, although the optimum level has not been determined and its beneficial effect appears to be readily overwhelmed by the presence of other risk factors. A family history of CHD is a positive risk factor, independent of diet and other risk factors. Hostility, anxiety or depression are associated with increased CHD and death, especially after myocardial infarction when mortality is doubled by anxiety and quadrupled by depression.

Epidemiological studies have shown associations between CHD and prior infections with several common microorganisms, including *Chlamydia pneumoniae* and *Helicobacter pylori*, but a causal connection has not been shown. The influence of fetal and infant growth conditions, and their interaction with social conditions in childhood and adult life, has been debated strongly for decades but it is clear that lower socio-economic status and thinness in very early life are linked to higher incidences of CHD.

Aetiology

The vast majority of CHD occurs in patients with atherosclerosis of the coronary arteries (see Fig. 20.1) that starts before adulthood. The cause of spontaneous artherosclerosis is unclear, although it is thought that in the presence of hypercholesterolaemia, a non-denuding form of injury occurs to the endothelial lining of coronary arteries and other vessels. This injury is followed by subendothelial migration of monocytes and the accumulation of fatty streaks containing lipid-rich macrophages and T-cells. Almost all adults, and 50% of children aged 11–14 years, have fatty streaks in their coronary arteries. Thereafter, there is migration and proliferation of smooth muscle cells into the intima with further lipid deposition. The smooth muscle cells, together with fibroblasts, synthesise and secrete collagen, proteoglycans, elastin and glycoproteins that make up a fibrous cap surrounding cells and necrotic tissue, together called a plaque. The presence of atherosclerotic plaques results in narrowing of vessels and a reduction in blood flow and a decrease in the ability of the

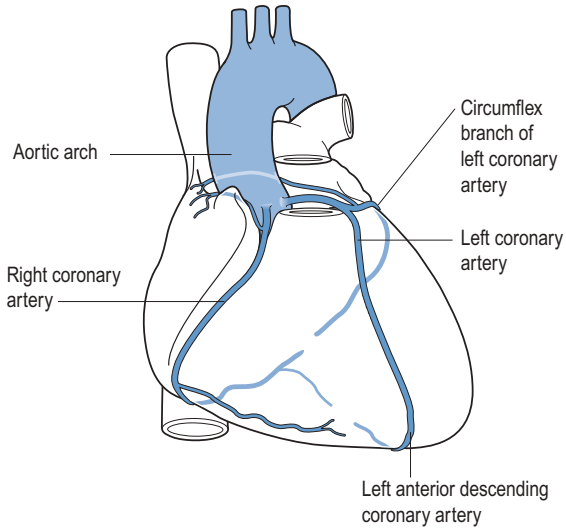

Fig. 20.1 Main coronary arteries.

coronary vasculature to dilate and this may become manifest as angina. Associated with the plaque rupture is a loss of endothelium. This can serve as a stimulus for the formation of a thrombus and result in more acute manifestations of CHD, including unstable angina (UA) and myocardial infarction. Plaque rupture caused by physical stresses or plaque erosion may precipitate an acute reaction. Other pathological processes are probably involved, including endothelial dysfunction which alters the fibrin–fibrinolysis balance and the vasoconstriction–vasodilation balance. There is interest in the role of statins and angiotensin-converting enzyme (ACE) inhibitors in modifying endothelial function.

There is also great interest in the role of inflammation, especially in acute episodes. At postmortem, many plaques are found to contain inflammatory cells and inflammatory damage is found at the sites of plaque rupture.

Measurement of acute phase inflammatory reactions, such as fibrinogen and CRP, has a predictive association with coronary events. High-sensitivity CRP assays have been used in populations without acute illness to stratify individuals into high-, medium- and low-risk groups. In patients with other risk factors, however, CRP adds little prognostic information. CRP is produced by atheroma, in addition to the major producer which is the liver, and is an inflammatory agent as well as a marker of inflammation. Evidence is emerging that drug therapy which reduces CRP in otherwise healthy individuals reduces the incidence of major cardiac events (Ridker, 2008).

Oxidative stress which involves the uncontrolled production of reactive oxygen species (ROS) or a reduction in antioxidant species has been linked in the laboratory to several aspects of cardiovascular pathogenesis including endothelial malfunction, lipid metabolism, atheroma formation and plaque rupture, but the clinical importance is unclear. The use of antioxidants has been disappointingly unsuccessful but there is interest in peroxisome proliferator-activated receptor (PPAR) agonists that modify ROS production; some of these are already in use for treating diabetes and are associated with favourable changes in many metabolic markers for CVD. Other agents that reduce ROS production include statins and drugs that reduce angiotensin production.

Modification of risk factors

Common to all stages of CHD treatment is the need to reduce risk factors (Table 20.1). The patient needs to appreciate the value of the proposed strategy and to be committed to a plan for changing their lifestyle and habits, which may not be easy to achieve after years of smoking or eating a particular diet. Preventing CHD is important but neither instant nor spectacular. It may require many sessions of counseling over several years to initiate and maintain healthy habits. It may also involve persuasion of patients to continue taking medication

Table 20.1 Effect of interventions on risk of myocardial infarction

Intervention	Control	Benefit of intervention
Stopping smoking for ≥5 years	Current smokers	50–70% lower risk
Reducing serum cholesterol		2% lower risk for each 1% reduction in cholesterol
Treatment of hypertension		2–3% lower risk for each 1 mmHg decrease in diastolic pressure
Active lifestyle	Sedentary lifestyle	45% lower risk
Mild to moderate alcohol consumption (approx. 1 unit/day)	Total abstainers	25–45% lower risk
Low-dose aspirin	Non-users	33% lower risk in men
Postmenopausal oestrogen replacement	Non-users	44% lower risk

The quality of data associated with these interventions varies greatly and figures may not apply to all patient groups.

for asymptomatic disorders such as hypertension or hyperlipidaemia. The general public, with government as its agent, need to agree that a reduction in the incidence of CHD is worth some general changes in lifestyle or liberty, for example, such as prohibiting the freedom to smoke in public. National campaigns to encourage healthy eating or exercise are expensive, as is the long-term medical treatment of hypertension or hyperlipidaemia, and such strategies must have the backing of governments to succeed. It has been argued that community-wide campaigns on cholesterol reduction have had measurable benefits in Finland, the USA and elsewhere, at least in high-risk, well-educated and affluent groups. It follows that the next challenge is to extend that success to poorer, ethnically diverse groups and to those portions of the population with mild-to-moderate risk.

For every individual there is a need to act against the causative factors of CHD. Thus, attempts should be made to control hypertension, heart failure, arrhythmias, dyslipidaemia, obesity, diabetes mellitus, thyroid disease, anaemia and cardiac valve disorders. Apart from medication, these will require careful attention to diet and exercise and will necessitate smoking cessation. Cardiac rehabilitation classes and exercise programmes improve many risk factors including obesity, lipid indices, insulin resistance, psychological state and lifestyle. They also impact on morbidity and mortality.

Epidemiological studies have suggested that antioxidants and hormone replacement therapy may be of benefit in preventing and treating coronary disease. Unfortunately, randomised clinical trials of vitamin E or hormone replacement therapy suggest that these agents are not of benefit and may indeed result in higher rates of cardiovascular events.

Clinical syndromes

The primary clinical manifestation of CHD is chest pain. Chest pain arising from stable coronary atheromatous disease leads to stable angina and normally arises when narrowing of the coronary artery lumen exceeds 50% of the original luminal diameter. Stable angina is characterised by chest pain and breathlessness on exertion; symptoms are relieved promptly by rest.

A stable coronary atheromatous plaque may become unstable as a result of either plaque erosion or rupture. Exposure of the subendothelial lipid and collagen stimulates the formation of thrombus which causes sudden narrowing of the vessel. The spectrum of clinical outcomes that result are grouped together under the term acute coronary syndrome (ACS) and characterised by chest pain of increasing severity either on minimal exertion or, more commonly, at rest. These patients are at high risk of myocardial infarction and death and require prompt hospitalisation. Many aspects of the treatment of stable angina and ACS are similar but there is a much greater urgency and intensity in the management of ACS.

Stable angina

Stable angina is a clinical syndrome characterised by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Characteristically, the discomfort (it is often not described by the patient as a pain) occurs after a predictable level of exertion, classically when climbing hills or stairs, and resolves within a few minutes on resting. Unfortunately, the clinical manifestations of angina are very variable. Many patients mistake the discomfort for indigestion. Some patients, particularly diabetics and the elderly, may not experience pain at all but present with breathlessness or fatigue; this is termed silent ischaemia.

Further investigations are needed to confirm the diagnosis and assess the need for intervention. The resting electrocardiogram (ECG) is normal in more than half of patients with angina. However, an abnormal ECG substantially increases the probability of coronary disease; in particular, it may show signs of previous myocardial infarction. Non-invasive testing is helpful. Exercise testing is useful both in confirming the diagnosis and in giving a guide to prognosis. Alternatives such as myocardial scintigraphy (isotope scanning) and stress echocardiography (ultrasound) provide similar information.

Coronary angiography is regarded as the gold standard for the assessment of CAD and involves the passage of a catheter through the arterial circulation and the injection of radio-opaque contrast media into the coronary arteries. The X-ray images obtained permit confirmation of the diagnosis, aid assessment of prognosis and guide therapy, particularly with regard to suitability for angioplasty and coronary artery bypass grafting.

Non-invasive techniques, including magnetic resonance imaging (MRI) and multi-slice CT scanning, are being developed and tested as alternatives to angiography.

Treatment of stable angina is based on two principles:

- Improve prognosis by preventing myocardial infarction and death.
- Relieve or prevent symptoms.

Pharmacological therapy can be considered a viable alternative to invasive strategies, providing similar results without the complications associated with percutaneous coronary intervention (PCI). An algorithm for addressing both these principles is outlined in Fig. 20.2. In addition, diabetes, hypertension and dyslipidaemia in patients with stable angina should be well controlled. Smoking cessation, without or with pharmacological support, and weight loss should be attempted.

Antithrombotic drugs

One of the major complications arising from atheromatous plaque is thrombus formation. This causes an increase in plaque size and may result in myocardial infarction. Antiplatelet agents, in particular aspirin, are effective in preventing platelet activation and thus thrombus formation. Aspirin is of proven benefit in all forms of established CHD, although the risk–benefit ratio in people at risk of CHD is less clear.

Aspirin. Aspirin acts via irreversible inhibition of platelet COX-1 and thus thromboxane production, which is normally complete with chronic dosing of 75 mg/day. This antiplatelet action is apparent within an hour of taking a dose of 300 mg. The effect on platelets lasts for the lifetime of the platelet.

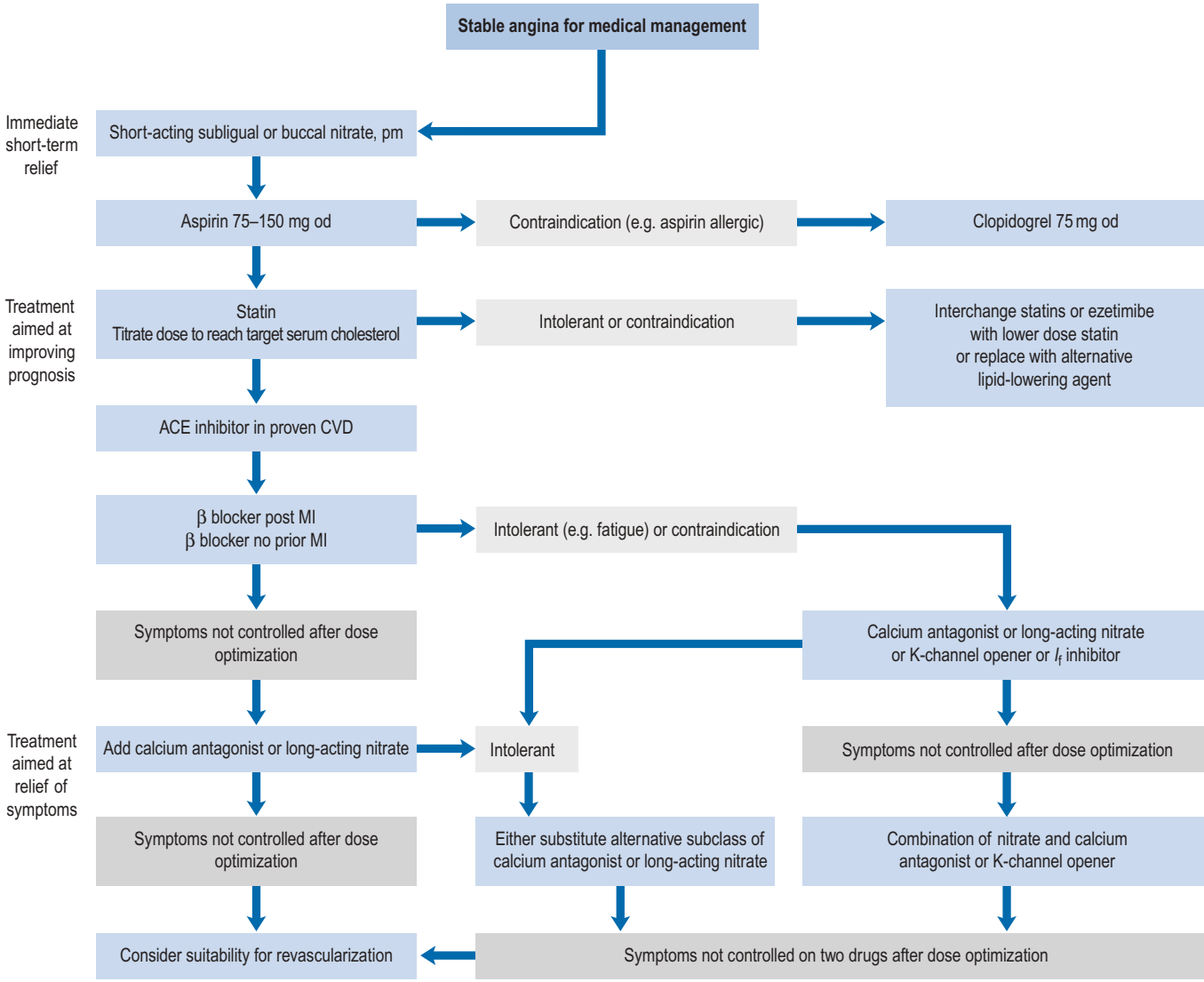

Fig. 20.2 Algorithm for the medical management of stable angina (Fox et al., 2006).

The optimal maintenance dose seems to be 75–150 mg day with lower doses having limited cardiac risk protection and higher doses increasing the risk of gastro-intestinal side effects. Dyspepsia is relatively common in patients taking aspirin and patients should be advised to take the medicine with or immediately after food. Enteric-coated preparations are no safer, and patients with ongoing symptoms of dyspepsia may require concomitant acid suppression with a proton pump inhibitor or switching to clopidogrel. Adverse reactions to aspirin include allergy, including bronchospasm. The benefits and risk of using aspirin in patients with asthma or a previous history of gastro-intestinal bleeding need to be carefully considered.

Clopidogrel. Clopidogrel inhibits ADP activation of platelets and is useful as an alternative to aspirin in patients who are allergic or cannot tolerate aspirin. Data from one major trial (CAPRIE Steering Committee, 1996) indicate that clopidogrel is at least as effective as aspirin in patients with stable coronary disease. The usual dose is 300 mg once, then 75 mg daily. Although less likely to cause gastric erosion and ulceration, gastro-intestinal bleeding is still a major complication of clopidogrel therapy. There is evidence that the combination of a proton pump inhibitor and aspirin is as effective as using clopidogrel alone in patients with a history of upper gastro-intestinal bleeding.

COX-2 inhibitors. The analgesic and anti-inflammatory action of non-steroidal anti-inflammatory drugs (NSAIDs) is believed to depend mainly on their inhibition of COX-2, and the unwanted gastro-intestinal effects of NSAIDs on their inhibition of COX-1. COX-2 inhibition reduces the production of prostacyclin, which has vasodilatory and platelet-inhibiting effects. Studies have raised concern about the cardiovascular safety of NSAIDs. Initially, the concern was focussed on the selective cyclo-oxygenase-2 inhibitors and a link to an increased cardiovascular risk. Recently, evidence has shown the more traditional non-selective NSAIDs increase

cardiovascular risk in both patients with established CVD and in the healthy population (Fosbol et al., 2010). NSAIDs with high COX-2 specificity increase the risk of myocardial infarction and should be avoided where possible in patients with stable angina.

ACE inhibitors

ACE inhibitors are established treatments for hypertension and heart failure, and have proven beneficial post myocardial infarction. In addition to the vasodilation caused by inhibiting the production of angiotensin II, ACE inhibitors have anti-inflammatory, antithrombotic and antiproliferative properties. Some of these effects are mediated by actions on vascular endothelium and might be expected to be of benefit in all patients with CAD. ACE inhibitors also reduce the production of ROS.

The use of ACE inhibitors in patients without myocardial infarction or left ventricular damage is based on two trials: the HOPE study (Yusuf et al., 2000) which studied ramipril and the EUROPA (2003) study which used perindopril. These trials also identified an incidental delay in the onset of diabetes mellitus in susceptible individuals which may be of long-term benefit to them. The HOPE study, a secondary prevention trial, investigated the effect of an ACE inhibitor on patients over 55 years old who had known atherosclerotic disease or diabetes plus one other cardiovascular risk factor. The use of ramipril decreased the combined endpoint of stroke, myocardial infarction or cardiovascular death by approximately 22%. The benefits were independent of blood pressure reduction. This has major implications for the management of CHD patients, both for the decision to treat all and the choice of treatment. At present the use of ACE inhibitors in patients with coronary disease, but without myocardial infarction, has general acceptance and is recommended in European guidelines.

Statins

Studies have repeatedly demonstrated the benefit of reducing cholesterol, especially low-density lipoprotein-cholesterol (LDL-C), in patients with CHD.

Earlier studies focused on patients with 'elevated' cholesterol, but all patients with coronary risk factors benefit from reduction of their serum cholesterol level. It is now clear that there is no 'safe' level of cholesterol for patients with CAD and that there is a continuum of risk down to very low cholesterol levels. Levels of LDL-C of <2 mmol/L and total cholesterol <4 mmol/L are recommended for patients with established CVD (NICE, 2008). Statins should be prescribed alongside lifestyle advice for both primary prevention of CVD and in those with established CVD (see Chapter 24 for more detail).

In addition to cholesterol-lowering properties, statins also have antithrombotic, anti-inflammatory and antiproliferative properties. They are also important in restoring normal endothelial function and inhibit the production of ROS in the vessel wall. There is some evidence that patients with elevated levels of CRP have better outcomes with statin therapy even if cholesterol levels are not raised. Most patients with stable angina will be on statins for their cholesterol-lowering effects. It is important, however, to recognise that these drugs may have beneficial effects independent of cholesterol lowering and this makes them valuable even in patients with 'normal' cholesterol levels.

Symptom relief and prevention

In stable angina, much of the drug treatment is directed towards decreasing the workload of the heart and, to a lesser extent, improving coronary blood supply; this provides symptomatic relief and improves prognosis. Therapy to decrease workload is targeted at both decreasing afterload and controlling heart rate. Recent evidence suggests a prognostic benefit when the resting heart rate is controlled below 70 beats/min. Drug treatment is initiated in a stepwise fashion according to symptom relief and side effects. A number of patients will require a number of anti-anginal medicine to control their angina symptoms.

β-Blockers

Various studies have demonstrated the beneficial effect of β-blockers in angina and they are now considered first-line agents. β-Blockers reduce mortality both in patients who have suffered a previous myocardial infarction and in those with heart failure. They reduce myocardial oxygen demand by blocking β-adrenergic receptors, thereby decreasing the heart rate and force of left ventricular contraction and lowering blood pressure. The decreased heart rate not only reduces the energy demand on the heart but also permits better perfusion of the subendocardium by the coronary circulation. β-Blockers may also reduce energy-demanding supraventricular or atrial arrhythmias and counteract the cardiac effects of hyperthyroidism or phaeochromocytoma.

β-Blockers are particularly useful in exertional angina. Patients treated optimally should have a resting heart rate of around 60 beats/min. Although many patients may dislike the side effects of β-blockers, they should be urged to continue wherever reasonable. β-Blockers should be used with caution in patients with diabetes as the production of insulin is under adrenergic system control and thus their concomitant use may worsen glucose control. β-Blockers can also mask the symptoms of hypoglycaemia and patients in whom the combination is considered of value should be warned of this; however, most clinicians now believe that the benefits of taking β-blockers, even in diabetics, outweigh the risks and they are frequently prescribed.

While β-blockers are widely used, their tendency to cause bronchospasm and peripheral vascular spasm means that they are contraindicated in patients with asthma, and used with caution in chronic obstructive airways diseases and peripheral vascular disease as well as in acute heart failure and bradycardia.

Cardioselective agents such as atenolol, bisoprolol and metoprolol are preferred because of their reduced tendency to cause

bronchoconstriction, but no β-blocker is completely specific for the heart. Agents with low lipophilicity, for example, atenolol, penetrate the central nervous system (CNS) to a lesser extent than others, for example, propranolol, metoprolol, and do not so readily cause the nightmares, hallucinations and depression that are sometimes found with lipophilic agents, which should not be used in patients with psychiatric disorders. CNS-mediated fatigue or lethargy is found in some patients with all β-blockers, although it must be distinguished from that of myocardial suppression. β-Blockers should not be stopped abruptly for fear of precipitating angina through rebound receptor hypersensitivity. They are contraindicated in the rare Prinzmetal's angina where coronary spasm is a major factor.

All β-blockers tend to reduce renal blood flow, but this is only important in renal impairment. Drugs eliminated by the kidney (Table 20.2) may need to be given at lower doses in the renally impaired or in the elderly, who are particularly susceptible to the CNS-mediated lassitude. Drugs eliminated by the liver have a number of theoretical interactions with other agents that affect liver blood flow or metabolic rate, but these are rarely of clinical significance since the dose should be titrated to the effect. Likewise, although there is theoretical support for the use of agents with high intrinsic sympathomimetic activity (ISA) to reduce the incidence or severity of drug-induced heart failure, there is no β-blocker that is free from this problem, and clinical trials of drugs with ISA have generally failed to show any extra benefit.

Calcium channel blockers

Calcium channel blockers (CCBs) act on a variety of smooth muscle and cardiac tissues and there are a large number of agents which have differing specificities for different body tissues.

Table 20.2 Properties and pharmacokinetics of β-blockers

	Blockade	Lipophilicity	ISA	Oral absorption	Elimination
Acebutolol	β_1 (some β_2)	+	+	90%[a]	Active metabolite ($t_{1/2}$ 11–13 h, renal)
					Gut 50%, $t_{1/2}$ 3–4 h
Atenolol	β_1	–	–	50%	Renal $t_{1/2}$ 5–7 h
Betaxolol	β_1	+	–	100%	Hepatic + renal $t_{1/2}$ 15 h
Bisoprolol	β_1	+	–	90%	Hepatic + renal $t_{1/2}$ 10–12 h
Carteolol	$\beta_1\beta_2$	–	++	80%	Hepatic + renal $t_{1/2}$ 3–7 h
Carvedilol	$\beta_1\beta_2\alpha_1$	+	–	80%[a]	Hepatic + renal $t_{1/2}$ 4–8 h
Celiprolol	$\beta_1\alpha_2$	–	β_2+	30–70%	Renal + gut $t_{1/2}$ 5–6h
Esmolol	β_1	–	–	i.v.	Blood enzymes $t_{1/2}$ 9 min
Labetalol	$\beta_1\beta_2\alpha_1$	–	–	100%[a]	Hepatic $t_{1/2}$ 6–8 h
Metoprolol	β_1	+	–	95%[a]	Hepatic $t_{1/2}$ 3–4 h
Nadolol	$\beta_1\beta_2$	–	–	30%	Renal $t_{1/2}$ 16–18 h
Nebivolol	β_1	+	–	12–96%[b]	Hepatic $t_{1/2}$ 8–27 h[b]
Oxprenolol	$\beta_1\beta_2$	+	++	90%[a]	Hepatic + $t_{1/2}$ 1–2 h
Pindolol	$\beta_1\beta_2$	+	+++	90%	Hepatic + renal $t_{1/2}$ 3–4 h
Propranolol	$\beta_1\beta_2$	+	–	90%[a]	Hepatic $t_{1/2}$ 3–6 h
Sotalol	$\beta_1\beta_2$	–	–	70%	Renal $t_{1/2}$ 15–17 h
Timolol	$\beta_1\beta_2$	+	–	90%[a]	Hepatic + renal $t_{1/2}$ 3–4 h

All figures are approximate and subject to interpatient variability. Therapeutic ranges are not well defined.
ISA, intrinsic sympathomimetic activity; $t_{1/2}$, elimination half-life.
[a]Extensive first-pass metabolism may result in a significant decrease in bioavailability.
[b]Genetically determined groups of slow and fast metabolisers have been identified.

While short-acting dihydropyridine CCBs have been implicated in the exacerbation of angina due to the phenomenon of 'coronary steal', longer acting dihydropyridines, for example, amlodipine and felodipine or longer acting formulations, for example, nifedipine LA, have demonstrated symptom-relieving potential similar to β-blockers. Dihydropyridines have no effect on the conducting tissues and are effective arterial dilators, decreasing afterload and improving coronary perfusion but also causing flushing, headaches and reflex tachycardia. This may be overcome by combination with a β-blocker. The use of dihydropyridines in angina is based on efficacy in trials that have used surrogate markers such as exercise tolerance rather than mortality as the endpoint.

CCBs with myocardial rate control as well as vasodilatory properties, for example, diltiazem, and those with predominantly rate-controlling effects, for example, verapamil, have also been shown to improve symptom control, reduce the frequency of anginal attacks and increase exercise tolerance. They should be avoided in patients with compromised left ventricular function and conduction abnormalities. Verapamil and diltiazem are suitable for rate control patients in whom β-blockers are contraindicated on grounds of respiratory or peripheral vascular disease. They should be used with caution in patients already receiving β-blockers, as bradycardia and heart block have been reported with this combination.

CCBs have a particular role in the management of Prinzmetal's (variant) angina which is thought to be due to coronary artery spasm.

Nitrates

Organic nitrates are valuable in angina because they dilate veins and thereby decrease preload, dilate arteries to a lesser extent thereby decreasing afterload, and promote flow in collateral coronary vessels, diverting blood from the epicardium to the endocardium. They are available in many forms but all relax vascular smooth muscle by releasing nitric oxide, which was formerly known as endothelium-derived relaxing factor, which acts via cyclic GMP. The production of nitric oxide from nitrates is probably mediated by intracellular thiols, and it has been observed that when tolerance to the action of nitrates occurs, a thiol donor (such as *N*-acetylcysteine) may partially restore the effectiveness of the nitrate. Antioxidants such as vitamin C have also been used. While clinical trials have not established any mortality gain from the use of oral nitrate preparations, their role in providing symptom relief is well established.

Tolerance is one of the main limitations to the use of nitrates. This develops rapidly, and a 'nitrate-free' period of a few hours in each 24-h period is beneficial in maintaining the effectiveness of treatment. The nitrate-free period should coincide with the period of lowest risk, and this is usually night time, but not early morning, which is a high-risk period for infarction. Many patients receiving short-acting nitrates two or three times a day would do well to have their doses between 7 a.m. and 6 p.m. (say, 8 a.m. and 2 p.m. for isosorbide mononitrate), but this is generally not practised in UA where there is no low-risk period and where continuous dosing is used, with increasing doses if tolerance develops.

There are many nitrate preparations available, including intravenous infusions, conventional or slow-release tablets and capsules, transdermal patches, sublingual tablets and sprays and adhesive buccal tablets. Slow-release preparations and transdermal patches are expensive, do not generally offer such flexible dosing regimens as short-acting tablets. Sustained release tablets do not release the drug over the whole 24-h period producing a 'nitrate free period', whereas patches need to be removed for a few hours each day. Buccal tablets are expensive and offer no real therapeutic advantage in regular therapy. Like sublingual sprays and tablets, however, they have a rapid onset of action and the drug bypasses the liver, which has an extensive first-pass metabolic effect on oral nitrates. The sublingual preparations, whether sprays or suckable or chewable tablets, are used for the prevention or relief of acute attacks of pain but may elicit the two principal side effects of nitrates: hypotension with dizziness and fainting, and a throbbing headache. To minimise these effects, patients should be advised to sit down, rather than lie or stand, when taking short-acting nitrates, and to spit out or swallow the tablet once the angina is relieved. Sublingual glyceryl trinitrate (GTN) tablets have a very short shelf-life on exposure to air, need to be stored carefully and replaced frequently. As a consequence they are now little used. All nitrates may induce tachycardia.

Three main nitrates are used: GTN (mainly for sublingual, buccal, transdermal and intravenous routes), isosorbide dinitrate and isosorbide mononitrate. All are effective if given in appropriate doses at suitable dose intervals (Table 20.3). Since isosorbide dinitrate is metabolised to the mononitrate, there is a preference for using the more predictable mononitrate, but this is not a significant clinical factor. A more relevant feature may be that whereas the dinitrate is usually given three or four times a day, the mononitrate is given once or twice a day. Slow-release preparations exist for both drugs.

Nicorandil

Nicorandil is a compound that exhibits the properties of a nitrate but which also activates ATP-dependent potassium channels. The IONA Study Group (2002) compared nicorandil with placebo as 'add-on' treatment in 5126 high-risk patients with stable angina. The main benefit for patients in the nicorandil group was a reduction in unplanned admission to hospital with chest pain. The study did not tell us when to add nicorandil to combinations of antianginals such as β-blockers, CCBs and long-acting nitrates. There is a theoretical benefit from these agents in their action to promote ischaemic preconditioning. This phenomenon is seen when myocardial tissue is exposed to a period of ischaemia prior to sustained coronary artery occlusion. Prior exposure to ischaemia renders the myocardial tissue more resistant to permanent damage. This mechanism is mimicked by the action of nicorandil.

Table 20.3 Properties of commonly used nitrates

Drug	Speed of onset	Duration of action	Notes
Glyceryl trinitrate (GTN)			
Intravenous	Immediate	Duration of infusion	
Transdermal	30 min	Designed to release drug steadily for 24 h	Tolerance develops if applied continuously
SR tablets and capsules	Slow	8–12 h	
Sublingual tablets	Rapid (1–4 min)	<30 min	Inactivated if swallowed Less effective if dry mouth
Spray	Rapid (1–4 min)	<30 min	
Buccal tablets	Rapid (1–4 min)	4–8 h	Nearly as rapid in onset as sublingual tablets
Isosorbide dinitrate			
SR tablets	Similar to GTN		
Intravenous	Similar to GTN		
Sublingual	Slightly slower than GTN	As for GTN	
Chewable tablets	2–5 min	2–4 h	Less prone to cause headaches than sublingual tablets
Oral tablets	30–40 min	4–8 h	
Isosorbide mononitrate			
Oral tablets	30–40 min	6–12 h	
SR tablets or capsules	Slow	12–24 h	Some brands claim a nitrate-free period if given once daily

SR, sustained-release.

Ivabradine

Ivabridine represents a class of antianginal agents which block the I_f current. I_f is a mixed Na^+–K^+ inward current activated by hyperpolarisation and modulated by the autonomic nervous system. This regulates pacemaker activity in the sinoatrial node and controls heart rate. Inhibition, therefore, reduces heart rate without affecting the force of contraction. Ivabridine is similar in efficacy to atenolol and CCBs and may be of particular use in patients in whom β-blockers are contraindicated. The most frequent adverse drug reactions are dose-dependent transient visual symptoms that manifest as transient enhanced brightness commonly associated with abrupt changes in light intensity. They may be related to the action of ivabradine at hyperpolarisation-activated, cyclic nucleotide-gated cation current channels present in the retina. Visual symptoms may resolve spontaneously during therapy or after drug discontinuation.

Ranolazine

Ranolazine, a selective inhibitor of late sodium influx, attenuates the abnormalities of ventricular repolarisation and contractility associated with ischaemia. It has been shown to increase exercise tolerance, reduce anginal episodes and reduce the use of GTN. Side effects include dizziness, constipation, nausea, and the potential for prolongation of the QTc interval. Ranolazine seems to be a safe addition to current traditional drugs for chronic stable angina, especially in aggressive multidrug regimens.

Acute coronary syndrome

Definition and cause

The group of conditions referred to as ACS often present with similar symptoms of chest pain which is not, or only partially, relieved by GTN. These conditions include acute myocardial infarction (AMI), UA and non-ST-elevation myocardial infarction (NSTEMI). AMI with persistent ST segment elevation on the ECG usually develops Q waves, indicating transmural infarction. UA and NSTEMI present without persistent ST segment elevation and are managed differently, although a similar early diagnostic and therapeutic approach is employed. All patients with ACS should be admitted to hospital for evaluation, risk stratification and treatment. The spectrum of ACS is described in Fig. 20.3.

ACS arises from the rupture of an unstable atheromatous plaque. This exposes the cholesterol-rich plaque in the intima to the blood, initiating platelet activation and eventual thrombus formation. The volume of the eventual thrombus and the time the vessel is occluded determine the degree of myocardial necrosis that occurs. The major difference in approach to these patients arises from whether the coronary artery involved is felt to be occluded or open.

Patients with an occluded coronary artery suffer myocardial damage, the extent of which is determined by the duration and site of the occlusion. The primary strategy for these patients is the restoration of coronary flow with either a fibrinolystic agent or primary angioplasty. If the coronary artery is patent, however, then fibrinolysis is unnecessary and probably harmful, although

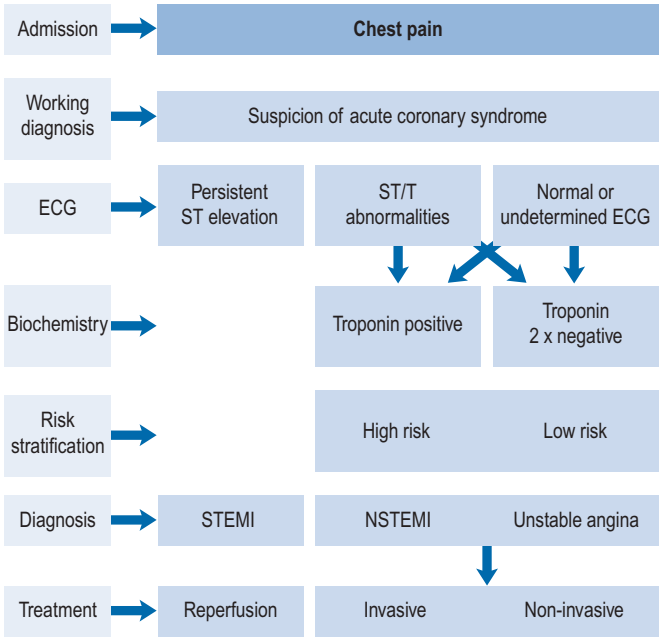

Fig. 20.3 The spectrum of acute coronary syndrome (Thygesen et al., 2007).

angioplasty may still be appropriate. When the vessel is open, for both groups, patient management focuses on the unstable coronary plaque and is, therefore, fundamentally similar.

Troponins (troponin I or troponin T) are cardiac muscle proteins which are released following myocardial cell damage and are highly sensitive and specific for myocardial infarction. They are useful in diagnosing patients with ACS and for predicting response to drug therapy; they are now key to the management of these patients and have replaced cardiac enzymes such as creatinine kinase (CK), aspartate transaminase (AST) and lactate dehydrogenase (LDH).

Diagnostic criteria for AMI have changed to incorporate the increasing availability of new diagnostic techniques with traditional symptoms and ECG changes. The following criteria for AMI, agreed by the European Society of Cardiology, rely on the rise of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following symptoms of ischaemia:

- ECG changes indicative of new ischaemia: new ST changes (STEMI or new left bundle branch block (LBBB))
- Development of pathological Q waves in the ECG
- Image evidence of new loss of viable myocardium or new regional wall motion abnormality.

Mortality rates of patients with presumed myocardial infarction or ACS in the first month is approximately 50% and of these deaths about half occur within the first 2 h. The prognosis of an individual who has suffered a STEMI and receives hospital treatment has improved following the widespread use of thrombolytic therapy and primary percutaneous intervention

The most dangerous time after a myocardial infarction is the first few hours when ventricular fibrillation (VF) is most likely to occur.

Patients without persistent ST elevation on the ECG may still have experienced myocardial damage due to temporary occlusion of the vessel or emboli from the plaque-related thrombus blocking smaller distal vessels and will have raised levels of troponin. These patients have had a NSTEMI. Patients without ST elevation and without a rise in troponin or cardiac enzymes are defined as having UA. The long-term prognosis in NSTEMI is similar to that of STEMI. The early adverse event rate is lower but these patients are more likely to suffer death, recurrent myocardial infarction or recurrent ischaemia after hospital discharge than patients with STEMI. More emphasis is now placed on improving the treatment of patients with NSTEMI than was previously the case.

The Global Registry of Acute Coronary Events (GRACE; available at http://www.outcomes-umassmed.org/GRACE/) is an international registry which has enrolled patients with ACS (UA, NSTEMI and STEMI) since 1999. The registry indicates a similar incidence of UA, NSTEMI and STEMI.

The classification of ACS based on ECG findings and measurement of troponin is shown in Fig. 20.4.

Treatment of ST elevation myocardial infarction

Treatment of STEMI may be divided into three categories:

- provide immediate care to alleviate pain, prevent deterioration and improve cardiac function;
- manage complications, notably heart failure and arrhythmias;
- prevent further infarction or death (secondary prophylaxis).

The management of heart failure and arrhythmias are covered more extensively in Chapters 21 and 22, respectively, and will not be discussed here. The remaining therapeutic aims are to relieve pain, return patency to the coronary arteries, minimise infarct size, provide prophylaxis to arrhythmias and institute secondary prevention.

Immediate care to alleviate pain, prevent deterioration and improve cardiac function

Pain relief. Patients with suspected STEMI should receive sublingual GTN under the tongue, oxygen administered and intravenous access established immediately. If sublingual GTN fails to relieve the chest pain, intravenous morphine may be administered together with an antiemetic such as prochlorperazine or metoclopamide. There is no benefit in leaving a patient in pain while the diagnosis is considered. Pain is associated with sympathetic activation, which causes vasoconstriction, increases the workload of the heart and can exacerbate the underlying condition.

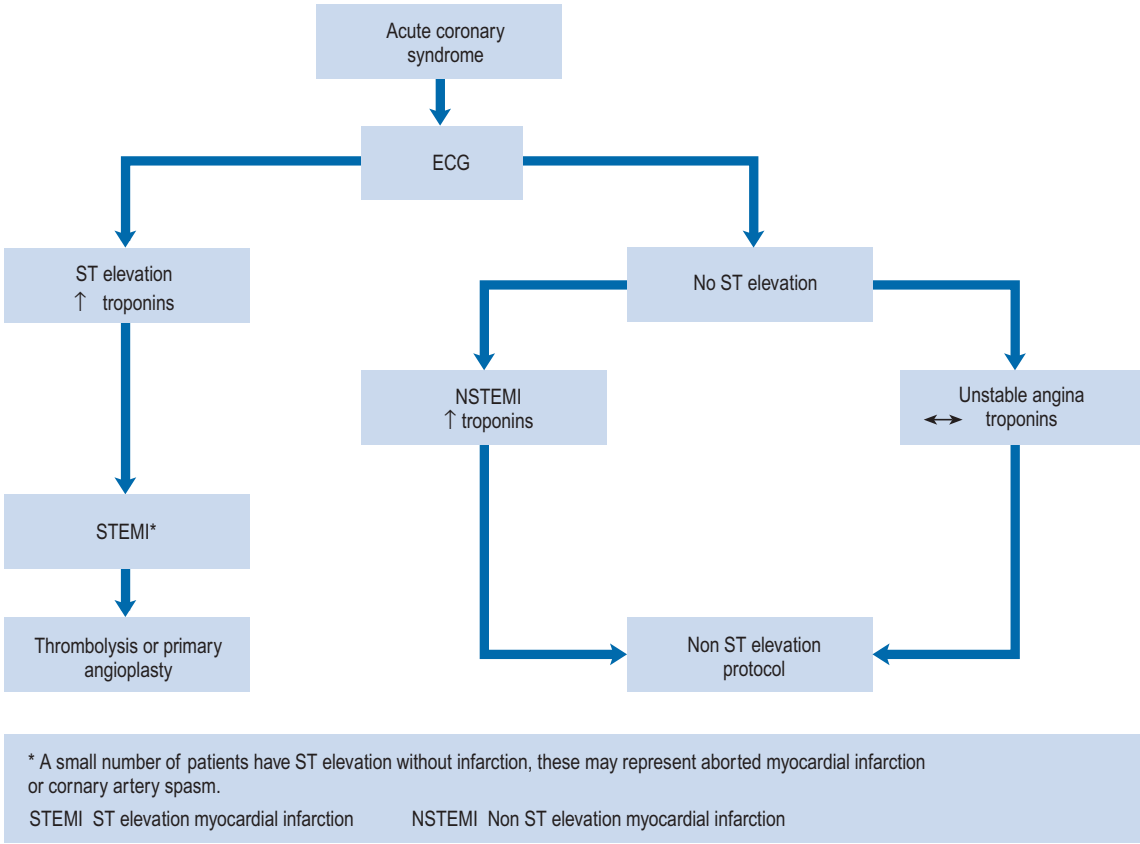

Fig. 20.4 Classification of ACS based on ECG and measurement of troponins.

Antiplatelet therapy. An aspirin tablet chewed as soon as possible after the infarct and followed by a daily dose for at least 1 month has been shown to reduce mortality and morbidity. Follow-up studies have demonstrated additional benefit in continuing to take daily aspirin, probably for life. The reduction in mortality is additional to that obtained from thrombolytic therapy (Table 20.4). Clopidogrel, given in addition to aspirin, can further improve coronary artery blood flow but the additional absolute reduction in mortality is small, at approximately 0.4% (Sabatine et al., 2005). In suspected heart attack patients in the UK, both aspirin and clopidogrel may be administered by the ambulance crew.

Restoring coronary flow and myocardial tissue perfusion

In patients with STEMI, early restoration of coronary artery patency results in an improved outcome; this may occur spontaneously in some patients but frequently only after substantial myocardial damage has occurred. Clinical trial data indicate that hospital mortality at 1 month has been reduced from 16% to 4–6% with the widespread use of coronary interventions, fibrinolytic agents and secondary prevention. In practice, available data suggest a higher mortality than that recorded in clinical trials.

Table 20.4 Vascular deaths at 35 days in the ISIS-2 study (1990)

Placebo	13.2%
Aspirin	10.7%
Streptokinase	10.4%
Aspirin + streptokinase	8.0%

The timing of treatment is vital, since myocardial damage after onset of an acute ischaemic episode is progressive and there are pathological data to suggest it is irreversible beyond 6 h. Clinical data from large studies of fibrinolysis have shown that the sooner treatment is started after the onset of pain, the better. All trials show that rapid treatment is important and this has a greater effect than the choice of drug; several studies indicate that giving fibrinolytics an average of 30–60 min earlier can save 15 lives per 1000 treated. Hospitals need to maintain fast-track systems to ensure maximum benefit, although there is still some worthwhile benefit up to 12 h after infarction.

Treatment within 1 h has been found to be particularly advantageous, although difficult to achieve, for logistical reasons, in anyone who has an infarct outside hospital. Prioritisation of ambulances to emergency calls for chest pain and appropriately equipped paramedics or primary care doctors administering fibrinolytics out of hospital have all helped reduce delay in fibrinolysis administration. Increased numbers of and direct access to hospitals offering primary angioplasty sites has further reduced the time to myocardial tissue reperfusion. Current reperfusion strategies are outlined in Fig. 20.5.

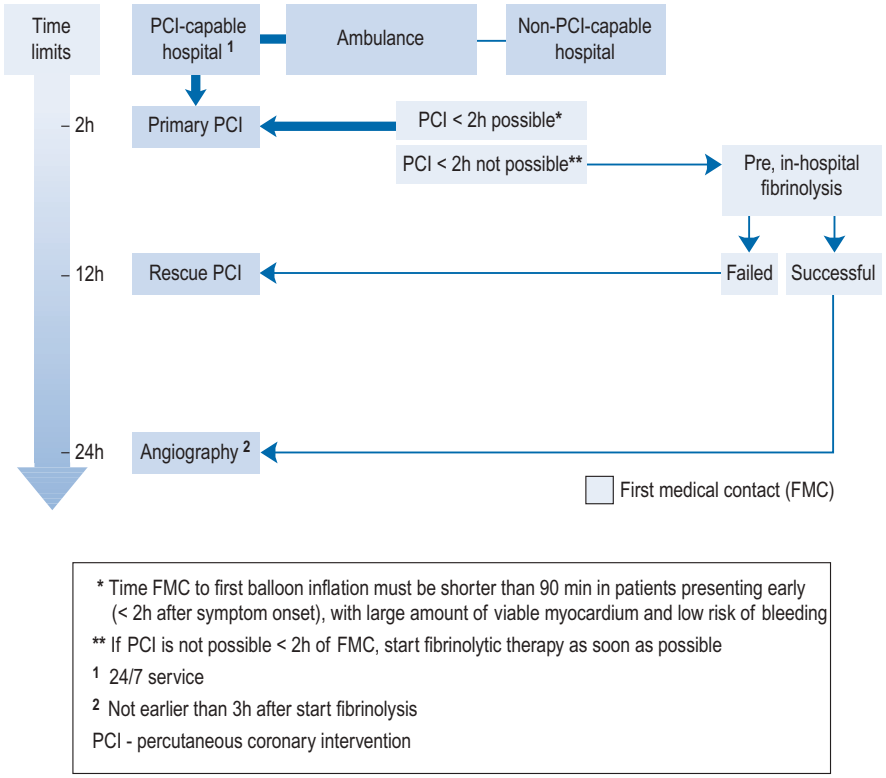

Fig. 20.5 Reperfusion strategies. The thick arrow (dark blue) indicate the preferred strategy (Van de Werf, 2008).

Fibrinolytics. Fibrinolytic agents (Table 20.5) have transformed the management of these patients by substantially improving coronary artery patency rates which has translated into a 25% relative reduction in mortality. The risk of haemorrhagic stroke (around 1%) and a failure to adequately reperfuse the affected myocardium in approximately 50% of cases have remained despite advances in fibrinolytics.

Percutaneous coronary intervention. The introduction of primary PCI (angioplasty and/or stent insertion without prior or concomitant fibrinolytic therapy) has demonstrated superiority to fibrinolysis when it can be performed expeditiously by an experienced team in a hospital with an established 24 h a day interventional programme. In this context, primary angioplasty is better than fibrinolysis at reducing the overall short-term death, non-fatal reinfarction and stroke. The target for time from first medical contact to first balloon inflation should be less than 2 h. If the delay to angioplasty is likely to be longer than 2 h, facilitated PCI can be undertaken.

Facilitated PCI involves use of a fibrinolytic to achieve reperfusion prior to a planned PCI. This approach allows the clinical team to bridge an anticipated delay in undertaking a PCI.

Rescue PCI is performed on coronary arteries which remain occluded despite attempts at fibrinolysis. It has better outcomes than repeated fibrinolytic therapy or conservative management.

PCIs encompass various invasive procedures to improve myocardial blood delivery by opening up the blood vessels. PCIs open stenosed coronary vessels and are less invasive than coronary bypass surgery, where the coronary vessels are replaced.

A percutaneous (through the skin) transluminal (through the lumen of the blood vessels) coronary (into the heart) angioplasty (surgery or repair of the blood vessels) (PTCA) was first carried out on a conscious patient in 1977. Now over 2 million people a year undergo PCIs. The procedure is less invasive than coronary artery bypass graft (CABG) surgery.

PCI involves the passing of a catheter via the femoral or radial artery and aorta into the coronary vasculature under

Table 20.5 Fibrinolytic agents (thrombolytics)

	Fibrin specificity	Elimination	Half-life (min)	Dosing	Antigenic	Mode of action
Streptokinase		Hepatic	18–23	1 h infusion	Yes	Activator complex
Alteplase	++	Hepatic	3–8	Bolus + 90 min infusion	No	Direct
Reteplase	+	Renal	15–18	Two boluses	No	Direct
Tenecteplase	+++	Hepatic	20–28	One bolus	No	Direct

radio-contrast guidance. Inflation of a balloon at the end of the catheter in the area of the atheromatous plaques opens the lumen of the artery. For patients undergoing PCI there is a small risk of death, myocardial infarction and long-term restenosis. This is reduced by insertion of a coronary artery stent and the use of pre- and peri-procedural antiplatelet therapy. Over the last 10 years the proportion of patients undergoing PCI and stent insertion has accounted for >95% of all PCI procedures.

Antiplatelet and anticoagulant therapy. After stent insertion there is a short-term risk of thrombus formation until the endothelial lining of the blood vessel has been re-established. The combination of clopidogrel (600 mg initiated pre-procedure and 75 mg daily thereafter) and aspirin has been shown to reduce the risk of myocardial infarction and need for reperfusion therapy and decrease the length of hospital stay.

Patients undergoing primary PCI should receive aspirin and clopidogrel as early as possible. Antiplatelet naïve patients should receive 300 mg of aspirin and 600 mg of clopidogrel. In the UK and elsewhere in Europe, these are administered by paramedics. Prasugrel has less metabolic activation steps and has a faster and more reliable onset of antiplatelet action. In combination with aspirin, it is recommended (NICE, 2009) for preventing atherothrombotic events in individuals undergoing PCI only when:

- immediate primary PCI for STEMI is necessary;
- stent thrombosis has occurred during clopidogrel treatment; and
- the individual has diabetes mellitus.

Heparin is routinely administered during the PCI procedure and is titrated to maintain an activated clotting time (ACT) of 250–350 s. Glycoprotein IIb/IIIa receptor antagonists, particularly abciximab, have been shown to reduce mortality if used during the procedure. These are used in combination with heparin, and a lower ACT (200–250 s) is targeted to reduce bleeding complications. Bivalirudin, a direct thrombin inhibitor, has demonstrated less bleeding compared to abciximab and may be useful in those at risk of increased bleeding.

Much of the evidence for the use of glycoprotein IIb/IIIa receptor antagonists was accumulated before high-dose clopidogrel or more potent antiplatelets were in routine practice. Current recommendations are that in the setting of dual-antiplatelet therapy with unfractionated heparin or bivalirudin as the anticoagulant, glycoprotein IIb/IIIa receptor antagonists can be useful at the time of primary PCI but cannot be recommended as routine therapy.

Intracoronary administration of vasodilators such as adenosine, verapamil, nicorandil, papaverine, and nitroprusside during and after primary PCI has been shown to improve flow in the infarct-related coronary artery and myocardial perfusion, and/or to reduce infarct size, but large prospective randomised trials with hard clinical outcomes are missing.

Fibrinolytics. Fibrinolytic agents fall into two categories: fibrin specific (alteplase, tenecteplase and reteplase) and fibrin non-specific (streptokinase). There are theoretical advantages for the fibrin-specific agents which are superior in terms of achieving coronary artery patency in angiographic studies. Angiographic patency has been shown to correlate well with outcome in thrombolytic trials but it has been difficult to prove that this benefit translates into an improvement in mortality. Studies have demonstrated considerable benefit from fibrinolytics given soon after the onset of pain but little difference between streptokinase and the more expensive tissue plasminogen activator (alteplase) in reducing mortality. Fast injection of fibrin-specific agents is better than slower infusion of streptokinase, especially in younger patients with anterior infarcts. Tenecteplase and reteplase have the advantage that they can be administered by bolus injection, which facilitates pre-hospital administration and reduces errors.

Patients receiving alteplase also receive a 5000 unit heparin bolus followed by a 48-h infusion adjusted to maintain the activated partial thromboplastin time (APTT) in the therapeutic range. Intravenous enoxaparin followed by subcutaneous injections may be an alternative. Heparin has not been compared to placebo in trials of tenecteplase or reteplase but it is standard practice to use heparin with these agents. Heparin has no advantage in addition to streptokinase, which has a longer lasting and less specific fibrinolytic action.

A low dose of fondaparinux, a synthetic, indirect anti-Xa agent, has been found to be superior to placebo or heparin in preventing death and reinfarction in patients who received fibrinolytic therapy (OASIS-6 Trial Group, 2006).

Bivalirudin, a direct thrombin inhibitor, reduces reinfarction rates compared to heparin when given with streptokinase but has not been studied with fibrin-specific agents. This combination resulted in a non-significant increase in non-cerebral bleeding complications (HERO-2 Trial Investigators, 2001).

Trials using various dosing combinations of glycoprotein IIb/IIIa inhibitors with newer fibrinolytic agents have not found a regimen that increases overall survival (Menon et al., 2004).

All fibrinolytics cause haemorrhage, which may present as a stroke or a gastro-intestinal bleed, and there is an increased risk with regimens that use intravenous heparin. Recent strokes, bleeds, pregnancy and surgery are contraindications to fibrinolysis. Streptokinase induces cross-reacting antibodies which reduce its potency and may cause an anaphylactoid response. Patients with exposure to streptokinase, or with a history of rheumatic fever or recent streptococcal infection, should not receive the drug. The use of hydrocortisone to reduce allergic responses has fallen out of favour, but patients should be carefully observed for hypotension during the administration of streptokinase.

Old age is no longer considered to be a contraindication to fibrinolysis. Although the risks are greater, the benefit is also greater, but the doses of alteplase and tenecteplase need to be adjusted for body weight.

All the major trials have used specific ECG criteria for entry, usually ST elevation in adjacent leads or LBBB, and eliminated patients with major contraindications to fibrinolysis (Box 20.2). Confusion often arises about the term 'relative contraindication'. For example, systolic hypertension is common in AMI, so most protocols recommend lowering the blood pressure with either a β-blocker or intravenous nitrates before commencing fibrinolysis. An increasing number of

Box 20.2 Contraindications to fibrinolysis (Van de Werf, 2008)

Absolute contraindications
- Haemorrhagic stroke of unknown origin at any time
- Ischaemic stroke in preceding 6 months
- CNS damage or neoplasms
- Recent major trauma/surgery/head injury (within preceding 3 weeks)
- Gastro-intestinal bleed within the last month
- Known bleeding disorder
- Non-compressible punctures
- Aortic dissection

Relative contraindications
- Transient ischaemic attack in preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or within 1 week postpartum
- Advanced liver disease
- Active peptic ulcer
- Infective endocarditis
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mmHg)

patients are on warfarin and this again is regarded as a relative contraindication to fibrinolysis; thresholds for the use of fibrinolysis in patients on warfarin vary from an INR of 2–2.4. The use of fibrinolytic therapy in patients with relative contraindications should take into account the site of the myocardial infarction and the likely size of the infarction. For example, in patients with a large anterior myocardial infarction the benefits of fibrinolysis may outweigh risk. In patients where there is a serious concern regarding bleeding following fibrinolysis, primary angioplasty should be considered.

Management of complications

Heart failure. Heart failure during the acute phase of STEMI is associated with a poor short- and long-term prognosis. It should be managed with oxygen, intravenous furosemide and nitrates. More severe failure or cardiogenic shock (tissue hypoperfusion resulting from cardiac failure with symptoms of hypotension, peripheral vasoconstriction and diminished pulses, decreased urine output and decreased mental status) should be treated with inotropes and/or inter-aortic balloon pumps to maintain the systolic blood pressure above 90 mmHg. Invasive monitoring may be required.

Arrhythmias. Life-threatening arrhythmias such as ventricular tachycardia, sustained VF or atrio-ventricular block occur in about one fifth of patients presenting with a STEMI, although this is decreasing due to early reperfusion therapy. β-Blockers have been the subject of many studies because of their anti-arrhythmic potential and because they permit increased subendocardial perfusion. In studies undertaken prior to the widespread use of fibrinolytics, the early administration of an intravenous β-blocker was shown to limit infarct size and reduce mortality from early cardiac events. A post hoc analysis of the use of atenolol in the GUSTO-I trial and a systematic review (Freemantle et al., 1999) did not support the routine, early intravenous use of β-blockers and, therefore, oral β-blockers are started within 24 h of the event. If a β-blocker is contraindicated because of respiratory or vascular disorders, verapamil may be used, since it has been shown to reduce late mortality and reinfarction in patients without heart failure, although it shows no benefit when given immediately after an infarct. Diltiazem is less effective but may be used as an alternative. This is clearly not a class effect; other echannel blockers have produced different results and nifedipine increases mortality in patients following a myocardial infarction.

Initially, magnesium infusions looked promising when given early after infarction. However, in large trials (ISIS-4), no reductions in mortality were found making the routine use of magnesium inappropriate. Magnesium infusions are used, however, to correct low serum magnesium levels if cardiac arrhythmias are present.

Sinus bradycardia and heart block may also occur after a myocardial infarction and patients may require temporary or permanent pacemaker insertion.

Blood glucose. Patients with a myocardial infarction are often found to have high serum and urinary glucose levels, usually described as a stress response. The CREATE-ECLA trial (Mehta et al., 2005) studied more than 20,000 patients and showed a neutral effect of insulin on mortality, cardiac arrest and cardiogenic shock. Current guidelines do not support the routine use of insulin in STEMI in patients not previously known to be diabetic.

Up to 20% of patients who have a myocardial infarction have diabetes. Moreover, diabetic patients are known to do poorly after infarction, with almost double the mortality rate of non-diabetics. In these patients, an intensive insulin regimen, both during admission and for 3 months after, was found to save lives (Malmberg, 1997). However, the follow-up study (Malmberg et al., 2005) did not show any mortality benefit from intensive insulin therapy compared to standard therapy. In patients with diabetes, it appears reasonable, however, to continue to control blood glucose levels within the normal range immediately post-infarct.

Prevention of further infarction or death (secondary prophylaxis)

Lipid-lowering agents. Reduction of cholesterol through diet and use of lipid-lowering agents are effective at reducing subsequent mortality and morbidity in patients with established CAD. Patients with established CHD should be treated to ensure LDL-C is less than 2 mmol/L and total cholesterol less than 4 mmol/L (see Chapter 24). In patients with AMI or high-risk NSTEMI, there was a reduction in the combination end point of death, myocardial infarction, or documented UA requiring hospitalisation, revascularisation or stroke when patients were treated with high intensity statin (atorvastatin 80 mg) compared to standard statin therapy (Cannon et al., 2004). A meta-analysis of studies (Josan et al., 2008) reaffirmed the benefit of high intensity statin therapy especially in those patients with ACSs. An additional finding of particular interest was that the results were significant for the high intensity treatment arms despite approximately half of patients not achieving LDL-C of less than 2 mmol/L.

β-Blockers. Long-term use of a β-blocker has been shown in several studies to decrease mortality in patients in whom there is no contraindication. β-Blockade should be avoided in individuals with heart block, bradycardia, asthma, obstructive airways disease or peripheral vascular disease. One large cohort study compared low and high doses of β-blockers with no therapy and found benefit in all treated patients with similar survival rates but a lower heart failure rate in the low-dose group (Rochon et al., 2000).

Angiotensin-converting enzyme inhibitors. ACE inhibitors have been tried in various doses and durations and have proved beneficial in reducing the incidence of heart failure and mortality. In all but the earliest trials, patients were given an ACE inhibitor for 4–6 weeks and treatment continued in patients with signs or symptoms of heart failure or left ventricular dysfunction. The HOPE study (Yusuf et al., 2000) found that ramipril improved survival in all groups of patients with CHD and this has led clinicians to continue ACE inhibitors in all patients with a myocardial infarction over the age of 55 and in younger patients with evidence of left ventricular dysfunction. Contraindications to their use include hypotension and intractable cough.

There is considerable interest in focusing on the possible benefits of combining ACE inhibition with angiotensin II receptor blockers. Angiotensin blockade alone does not cause the accumulation of bradykinins that may be part of the benefit of using ACE inhibitors. Clinical trials (OPTIMAAL Study Group, 2002; VALIANT Investigators, 2003) have failed to find a benefit over ACE inhibition. Nonetheless, angiotensin receptor blockers are probably suitable in patients who cannot tolerate an ACE inhibitor. The relative benefits of ACE inhibitors and other treatments are shown in Table 20.6.

Eplerenone. In patients with heart failure, post-AMI, an improvement in survival and decreased cardiovascular mortality and hospitalisation was seen in those taking the aldosterone antagonist eplerenone (EPHESUS Trial; Pitt et al., 2003). Serious hyperkalemia occurred more frequently in the eplerenone arm and monitoring of serum potassium is warranted when used in practice.

Antidepressants. Anxiety is almost inevitable and a quarter of patients who have suffered a myocardial infarction subsequently experience marked depression. Post-myocardial infarction depression is associated with poor medication compliance, a lower quality-of-life score and a four-fold increase in mortality (Januzzi et al., 2000). Antidepressant treatments have not been subjected to formal trials but it seems reasonable to try to reduce the depression. There is concern about the potential for older antidepressants, such as tricyclic antidepressants, to increase the QT interval and cause arrhythmias. Newer antidepressants are less prone to cause these arrhythmias and selective seretonin receptor inhibitors (SSRIs) are preferred.

Rehabilitation programmes, which include some measure of social interaction, physical activity and education, are also of proven benefit. Although psychological stress clearly worsens outcomes, stress reduction interventions have not been tested and proven to work independently of other measures.

Nitrates. Studies on nitrates in myocardial infarction were mostly completed before fibrinolysis was widely used.

Table 20.6 Relative benefits of treating 1000 patients for myocardial infarction (MI)

Intervention	Events prevented
Intravenous β-adrenoceptor blocker	6 deaths
ACE inhibitor	6 deaths
Aspirin	20–25 deaths
Streptokinase (in hospital)	20–25 deaths
Alteplase (in hospital)	35 deaths
Streptokinase (before hospital)	35–40 deaths
Fibrinolysis 4½–1 h earlier	15 deaths
Long-term aspirin	16 deaths/MI/strokes
Long-term β-blockade	18 deaths/MI
Long-term ACE inhibitor	21–45 deaths/MI
10% reduction in serum cholesterol	7 deaths/MI
Stopping smoking	27 deaths

Adapted from McMurray and Rankin (1994).

Nitrates improve collateral blood flow and aid reperfusion, thus limiting infarct size and preserving functional tissue. ISIS-4 (1993) and GISSI-3 (1994) demonstrated that nitrates did not confer a survival advantage in patients receiving fibrinolysis. Sublingual nitrates may be given for immediate pain relief, and the use of intravenous or buccal nitrates can be considered in patients whose infarction pain does not resolve rapidly or who develop ventricular failure.

Anticoagulants and antiplatelets. Anticoagulation with warfarin is not generally recommended following a myocardial infarction, despite promising results in trials that have practiced exceptionally good anticoagulant monitoring. This is partly because of the success of antiplatelet therapy with aspirin. Aspirin does not have the same need for expensive and time-consuming follow-up and monitoring as warfarin, and is associated with fewer drug interactions. Clopidogrel has been shown to be beneficial, in addition to aspirin, in patients who have had a myocardial infarction (COMMIT, 2005). As the number of patients who receive a stent increases, the combination of aspirin and clopidogrel for a year or longer is now more frequent. Routine use of dipyridamole and sulfinpyrazone is not recommended after a myocardial infarction.

Treatment of non-ST elevation acute coronary syndromes

ACS without ST elevation is classified as either UA or NSTEMI. UA is defined as angina that occurs at rest or with minimal exertion, or new (within 1 month) onset of severe

angina or worsening of previously stable angina. NSTEMI (or non-Q wave MI) is the more severe manifestation of ACS.

There are about 115,000 new patients diagnosed each year with UA or NSTEMI in England and Wales. Despite the use of standard therapy the rate of adverse outcomes such as death, non-fatal MI or refractory angina requiring revascularisation, remains at 5–7% at 7 days and about 15–30% at 30 days; 5–14% of patient with UA or NSTEMI die within the first year of diagnosis.

There are extensive data for angioplasty following NSTEMI where patients frequently have significant residual coronary artery narrowing despite treatment with antiplatelet agents, heparin and glycoprotein IIb/IIIa antagonists.

Patients with NSTEMI may either be treated with an interventional strategy, where all patients undergo angiography and PCI following admission, or conservatively where they undergo angiography and intervention only if they remain unstable or have a positive exercise test. Initial trials of early intervention did not demonstrate any benefit but with the advent of advanced angioplasty techniques using stents and adjuvant drug therapies including clopidogrel and glycoprotein IIb/IIIa antagonists, there appears to be a clear advantage for an interventional strategy in high-risk patients (Fox et al., 2005).

Patients presenting with UA/NSTEMI can be classified into three categories depending on their risk of death or likelihood of developing an AMI. High-risk patients (those with ST segment changes during chest pain, chest pain within 48 h, troponin T-positive patients and those presenting already on intensive anti-anginal therapy) can be effectively managed with aggressive medical and interventional therapy. This results in fewer individuals progressing to AMI.

Various pharmacological agents such as antithrombin and antiplatelet drugs, and coronary revascularisation (particularly PCI) have been shown to improve the outcome of patients with UA or NSTEMI. These interventions are known to be associated with some treatment hazards, particularly bleeding complications. The risks must be balanced against potential treatment benefits for each individual patient. This balance is influenced by the patient's estimated risk of an adverse cardiovascular outcome as a consequence of the ACS. The absolute magnitude of benefit from an intervention is generally greatest in those at highest risk. A confounding issue is that treatment hazards, such as bleeding complications, are often also greatest in those at highest risk of an ischaemic event.

Measures of risk can be derived from the clinical assessment of a patient and the use of a formal risk scoring system, such as the GRACE, PURSUIT, PREDICT or TIMI scores. Scores based on clinical trial data generally exclude patients who are at high risk of an adverse cardiovascular outcome such as the elderly, or those with renal or heart failure, and as a consequence the evidence for clinical and cost-effectiveness of therapeutic interventions is confined to patients at lower to intermediate levels of risk. Risk score based on registry data, for example, GRACE, may provide a more realistic estimation of risk (Tables 20.7 and 20.8).

In patients with NSTEMI, the immediate administration of 300 mg aspirin can reduce mortality or subsequent myocardial infarction by 50%. Risk stratification according to a recognised tool should be used to guide the subsequent choice of pharmacological and/or surgical intervention. The exclusion of STEMI and confirmation of NSTEMI is important as the use of fibrinolysis in NSTEMI confers no benefit, and merely increases the risk of bleeding. In patients with NSTEMI, the preferred treatment normally involves a combination of antiplatelet agents to reduce the formation of a thrombus.

Antiplatelet and anticoagulant drugs

The current range of antiplatelet and anticoagulant drugs available for the reduction of thrombotic events in ACS leads to the potential for a large number of combinations. In all cases, the benefit of reducing thrombotic events must be balanced against the potential for an increased risk of bleeding.

In the early 1990s, unfractionated heparin, when combined with aspirin showed a reduction in death and subsequent myocardial infarction compared with aspirin alone. The use of the low molecular weight heparin (LMWH), enoxaparin, subsequently demonstrated superiority over unfractionated heparin, with both usually continued for 48 h, or until chest pain resolved or discharge. Both groups of drugs were tested in the era before PCI became part of routine practice.

The CURE study (2001) showed that clopidogrel, given as a loading dose of 300 mg followed by 75 mg daily in combination with aspirin and heparin, reduced the combined end point of death, myocardial infarction and revascularisation in all patients with NSTEMI. Clopidogrel needs to be continued for 12 months but should be stopped 5–7 days before any major surgery to reduce the risk of bleeding.

As PCI has become more routine as part of the management of high-risk NSTEMI patients, more aggressive antiplatelet treatment has been required to reduce both peri-procedural and post-procedural thromboembolic complications.

Expression of glycoprotein IIb/IIIa is one of the final steps in the platelet aggregation cascade. Inhibiting these receptors has been a strategy prior to, and during, PCI for some time. Glycoprotein IIb/IIIa inhibitors bind to the IIb/IIIa receptors on platelets (Fig. 20.6) and prevent cross-linking of platelets by fibrinogen. There are three classes of these agents: murine-human chimeric antibodies, for example, abciximab; synthetic peptides, for example, eptifibatide; and non-peptide synthetics, for example, tirofiban. Oral agents are ineffective and the murine-human chimeric antibodies appear to be effective only in the context of PCI.

In high-risk patients undergoing PCI and receiving background heparin, triple antiplatelet therapy (aspirin, clopidogrel and a glycoprotein IIb/IIIa inhibitors) has been shown to be superior to standard dose dual-antiplatelet therapy (aspirin and clopidogrel) particularly in troponin positive individuals (Kastrati et al., 2006). However, much of this evidence was generated before the introduction of higher doses of clopidogrel or more potent oral antiplatelet agents.

There is no clear benefit to giving glycoprotein IIb/IIIa inhibitors more than 4 h before PCI (upstream) compared to waiting until immediately before or during the procedure (deferred) (Stone et al., 2007).

Currently, all patients with a likely or definite diagnosis of NSTEMI should receive a loading dose of aspirin 300 mg (see Fig. 20.7). Patients undergoing PCI intervention should

Table 20.7 Classification of high-risk patients with NSTEMI as determined by the GRACE prediction score card and nomogram

GRACE Prediction Score Card

Risk calculator for in-hospital mortality for ACS with NSTEMI

Sum the points to calculate the total risk score. Correlate the score with the appropriate risk category (for all cause mortality during in-hospital stay as set out in Table 20.8).

Findings at initial hospital presentation				Findings during hospitalisation	
1		3		6	
Age (years)	Points	Resting heart rate (beats/min)	Points	Initial serum creatinine (μmol/L)	Points
<30	0	<50	0	0–34	1
30–39	8	50–69	3	35–70	4
40–49	25	70–89.9	9	71–105	7
50–59	41	90–109.9	15	106–140	10
60–69	58	110–149.9	24	141–176	13
70–79	75	150–199.9	38	177–353	21
80–89	91	>200	46	>354	28
>90	100				
2		4		7	
Killip class		Systolic blood pressure (mmHg)		Elevated cardiac enzymes	14
I. No clinical signs of HF	0	<80	58		
II. Rales and/or JVD	20	80–99.9	53		
III. Pulmonary oedema	39	100–119.9	43		
IV. Cardiogenic shock	59	120–139.9	34		
		140–159.9	24		
		160–199.9	10		
		>200	0		
		5		8	
		ST Segment deviation	28	Cardiac arrest on admission	39

(JVD, jugular venous distension)

have a higher loading dose of 600 mg of clopidogrel or 60 mg of prasugrel, unless contraindicated, to reduce events during and after PCI. Clopidogrel is often given as 300 mg on admission and a further 300 mg when the decision to intervene is made. Prasugrel, with its faster time to maximum effect, has demonstrated some benefit but routine use is not recommended (NICE, 2009). Patients who are not planned for intervention should receive a lower loading dose of clopidogrel 300 mg.

All patients should receive heparin, bivalirudin or fondaparinux. Unfractionated heparin is preferred for patients with compromised renal function. Fondaparinux, a synthetic pentasaccharide factor Xa inhibitor which has predictable and sustained anticoagulation with fixed dose, once-a-day subcutaneous administration, causes less bleeding than enoxaparin, an LMWH. Concerns over catheter related thrombus mean it should not be considered if patients are planned for PCI within 24 h of chest pain. Bivalirudin is a

Table 20.8 GRACE prediction nomogram for all cause mortality during in-hospital stay and up to 6 months post discharge

Risk category (tertiles)	GRACE risk score	In-hospital death (%)
Low	<109	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category (tertiles)	**GRACE risk score**	**Post-discharge to 6 months**
Low	<89	<3
Intermediate	89–118	3–8
High	>118	>8

GRACE Registry. Available at www.outcomes-umassmed.org/GRACE/index.cfm.

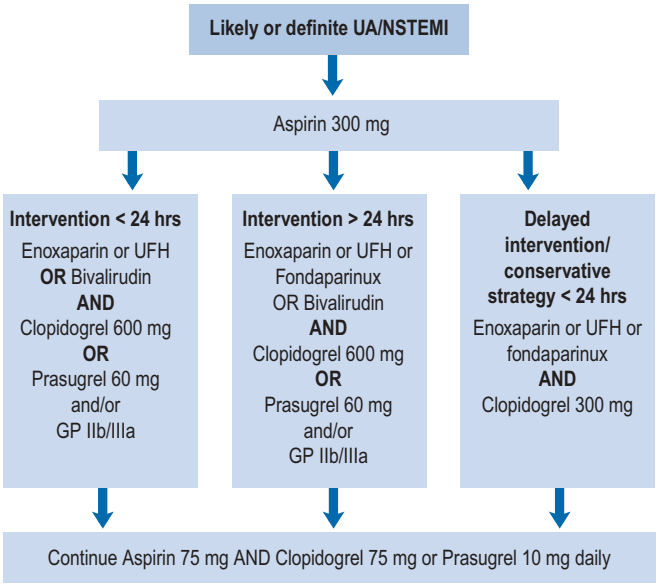

Fig. 20.7 Treatment options for patients with likely or definite unstable angina (UA) or NSTEMI in relation to time of PCI intervention.

synthetic analogue of hirudin that binds reversibly to thrombin and inhibits clot-bound thrombin and may be considered an alternative.

The decision to use glycoprotein IIb/IIIa inhibitors is dependant on the centre and operator and whether the planned intervention for the patient is to be surgical or pharmacological. The introduction of higher loading doses of clopidogrel and more potent oral agents, as well as an increased focus on the bleeding risks associated with combination therapy, has reduced the use of these agents in many centres.

Recommendation of an anticoagulant regimen has become more complicated by a number of new choices suggested by contemporary trials, some of which do not provide adequate comparative information for common practice settings.

Anti-ischaemic drugs

The use of both β-blockers and nitrates in the management of patients with NSTEMI is based on studies of their use in stable angina and AMI. Their use is, however, well established and based on a firm pathophysiological and pharmacological rationale.

Statins

High intensity statins have been shown to benefit patients when given early in ACS. They are usually started on admission if the diagnosis of CAD is definite, independent of the patient's cholesterol level. Treatment should aim to achieve total cholesterol of <4 mmol/L and an LDL-C of <2 mmol/L.

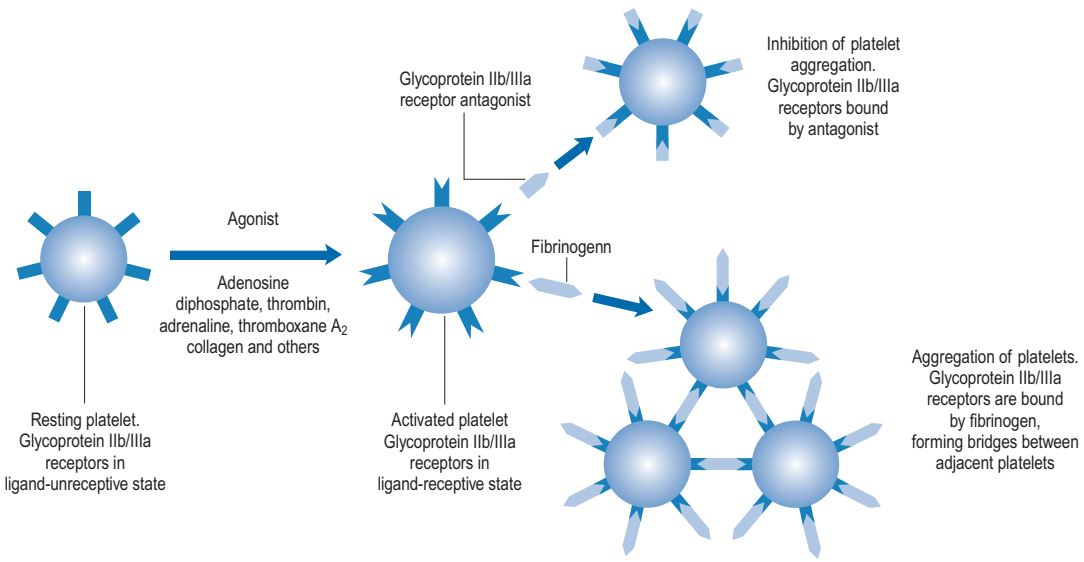

Fig. 20.6 Schematic representation of mechanism of action of glycoprotein IIb/IIIa inhibitors.

Patient care

Patients with CHD range from those who have investigational evidence of CHD but no symptoms to those who have major pain and exercise limitation. All need encouragement in adhering to preventive measures including diet, exercise and smoking cessation. Patients need to be able to discuss concerns about their health.

Exercise must be tailored according to the patient's threshold for angina. In general, although some patients are too cavalier, most are likely to err on the cautious side and may need to be encouraged to do more. Many centres now run cardiac rehabilitation classes to encourage patients to exercise and adopt a suitable lifestyle.

There are simple treatments and important lifestyle changes that can reduce cardiovascular risk and slow or even reverse progression of established coronary disease. The most important of these to address is smoking cessation. The risk of CHD is two to four times higher in heavy smokers (those who smoke at least 20 cigarettes/day) than in those who do not smoke. Other reports estimate the age-adjusted risk for smokers of more than 25 cigarettes/day is five to 21 times that of non-smokers. Smokers should be encouraged to quit. Within months of stopping smoking, CHD risk begins to decline. Within 5 years of smoking cessation the risk decreases to approximately the level found in people who have never smoked, regardless of the amount smoked, duration of the habit and the age at cessation. The use of nicotine replacement therapy almost doubles a smokers' chance of successfully stopping smoking (18% vs. 11%). All patients who smoke should be offered advice on cessation and encouraged to attend specialist smokers' clinics to further improve their chance of quitting.

Patient beliefs about medicines and medication-taking behaviour (and therefore adherence) are also important determinants of outcome and are influenced by many factors. These can largely be divided into beliefs about the importance of the medicine and concerns about the medicine's harmful effects. In order to assure the patient's concordance with medication regimens, it is necessary to address each individual patient's beliefs and concerns. One approach to counselling patients with CHD may be to divide the medication prescribed into those used to reduce risk of heart attacks and death, and those for symptom control. Key points to be discussed will relate to side effects and what to do if they occur, the need to continue medication until told otherwise and to ensure they do not run out of medication. Patients should be encouraged to identify their concerns and these should be addressed as openly and honestly as possible.

Patients also need up-to-date advice when faced with difficult choices regarding medical treatment, angiographic procedures or surgery. Patients have good reason to be anxious at times but some patients restrict their activities unnecessarily out of fear of angina and infarction.

Some of the common therapeutic problems encountered in the management of CHD are described in Table 20.9.

Table 20.9 Common therapeutic problems in coronary heart disease

Problem	Comment
Used incorrectly, nitrates may cause hypotensive episodes or collapse	Advise to sit down when using nitrate sprays or sublingual tablets
A daily nitrate-free period is required to maintain efficacy of nitrates	Avoid long-acting preparations and prescribe asymmetrically (e.g. 8 a.m. and 2 p.m.)
NSAIDs are associated with renal failure when given with ACE inhibitors	Warn patients to use paracetamol as their analgesic of choice
Speed is essential when patients need fibrinolytic drugs after infarction	Arrange emergency admission to hospital where fast-track systems should exist
Aspirin may cause gastro-intestinal bleeding	Advise on taking with food and water. Consider use of prophylactic agents in high-risk patients
β-Blockers are often considered unpleasant to take	Encourage patient to use regularly. Change the time of day. Consider a vasodilator if cold extremities are a problem. Consider verapamil or diltiazem
β-Blockers are contraindicated in respiratory and peripheral vascular disease	Consider verapamil or diltiazem. Pay strict attention to other treatments and removal of precipitating factors
Patients often receive multiple drugs for prophylaxis and for treatment of co-existing disorders	Use once-daily preparations, dosing aids and intensive social and educational support. Avoid all unnecessary drugs
ACE inhibitors are contraindicated in pregnancy, especially the first trimester	Advise women of child-bearing years to avoid conception or seek specialist advice first

Case studies

Case 20.1

A 55-year-old man presents to his primary care doctor complaining of tightness in his chest when he digs the garden. It eases when he has a rest. On investigation he has a raised serum glucose concentration and is considered to be a newly diagnosed non-insulin-dependent type II diabetic.

Question

What cardiovascular investigations and treatments should this patient receive?

Answer

The patient's blood pressure and ECG should be checked and he should be examined for signs of hypertensive or diabetic target organ damage, including albuminuria. His serum lipid profile should be measured.

He should receive GTN spray or sublingual tablets for the chest symptoms that are almost certainly angina. He should take aspirin daily and a statin if his lipid profile is abnormal. Some prescribers would give a statin in almost all diabetic, CHD patients and likewise an ACE inhibitor. Certainly, any hypertension should be treated aggressively so that the diastolic pressure is less than 80 mmHg. A β-blocker may also be useful to control blood pressure and prevent further episodes of angina, but many prescribers would wait until there was evidence of failure of the other therapies. In view of his relatively young age, a referral to a cardiologist for possible angiography would be considered. Dietary advice and help to stop smoking, if needed, would be given. Diabetic treatments should be given (see Chapter 44).

Case 20.2

The following patients are admitted for treatment of myocardial infarction:
1. an asthmatic
2. a man previously treated for infarction
3. a patient with rheumatoid arthritis.

Question

What contraindications, or possible contraindications, are there to standard treatments in the above patients?

Answers

1. An asthmatic should not receive a β-blocker without careful consideration and supervision because of the risk of bronchoconstriction; there is also a small risk of bronchoconstriction with aspirin.
2. A previous infarct may have been treated with streptokinase and a repeat dose should be avoided. Tissue plasminogen activator should be used instead.
3. Fibrinolytics are contraindicated if there is a serious risk of bleeding. A patient with rheumatoid arthritis may be receiving NSAIDs or steroids and enquiries must be made into any history of gastro-intestinal bleeding. NSAIDs would also not be prescribed with ACE inhibitors because of the risk of impaired renal function. Aspirin is not contraindicated with NSAIDs, and may be useful, but will increase the risk of gastro-intestinal bleeding.

Case 20.3

A patient with rheumatoid disease, treated with naproxen, has CHD.

Question

Is there any benefit or harm in adding aspirin to his treatment?

Answer

Aspirin is more beneficial than any other non-steroidal anti-inflammatory agent in modifying platelet activity and reducing mortality and morbidity in CHD. There is an increased risk of gastro-intestinal bleeding if two agents are given but at low doses of aspirin this should not be a major consideration. There is some evidence, however, that some NSAIDs interfere with the action of aspirin by blocking access to the active site on the COX-1 enzyme. Such agents should be avoided. Diclofenac does not block the receptor and ibuprofen has a short action and is acceptable if given 2 h after the daily dose of aspirin.

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