GASTROENTEROLOGY AND HEPATOLOGY

Lecture Notes

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Lecture Notes:

Gastroenterology and Hepatology

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Preface

Science is the father of knowledge, but opinion breeds ignorance.

(Hippocrates 460–357 BC)

Specialised knowledge will do a man no harm if he also has common sense; but if he lacks this he can only be more dangerous to his patients.

(Oliver Wendell Holmes 1809–1894)

The content of any textbook has, by definition, got to be factual. There are two potential consequences of this. The first, and most important, is that medical fact is based upon science, and we have based this book on the anatomical, physiological and pathological basis of gastrointestinal practice. The second potential consequence of a factual focus is that the text can become rather dry and list like. To limit this we have tried to present the information from a clinical perspective – as the patients present in outpatients or casualty.

Gastroenterology is well suited to such an approach. It is a fundamentally practical speciality, with a strong emphasis on history, examination and endoscopy. The importance of integrating clinical assessment with investigation – both anatomical and physiological – is emphasised by the curiously limited range of symptoms despite the complexity of the gastrointestinal tract. The gut contains about three-quarters of the body's immune cells; it produces a wider range of hormones than any single endocrine organ; it has almost as many nerves as the spinal cord; it regulates the daily absorption of microgram quantities of vitamins simultaneously with macronutrients in 100 million times that amount.

We have tried to combine a didactic approach to facts alongside recurrently occurring themes to aid memory. For example, we have referred to the principles of embryology of the gut to give a common sense reminder of how abdominal pain is referred and how the blood supply can be understood; approached lists of investigations by breaking them down to tests which establish the condition, the cause or the complications; approached aetiological lists by breaking down into predisposing, precipitating and perpetuating ones. We have eschewed 'introductory chapters' on anatomy, physiology and biochemistry as these are frequently skipped by readers who are often studying gastroenterology alongside some other subject. Rather, we have included preclinical material in the practical context of relevant disease areas (fluid absorption physiology in the section on diarrhoea, haemoglobin biochemistry in that on jaundice, etc.). Ultimately, we hope the reader uses this book as a source of material to help understand a fascinating speciality, pass exams in it, but above all be able to get as much as possible out of each patient seen with a gastrointestinal complaint.

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1

Approach to the patient with abdominal pain

In gastroenterological practice, patients commonly present complaining of abdominal pain. The clinician's role is to undertake a full history and examination, in order to discern the most likely diagnosis and to plan safe and cost-effective investigation. This chapter describes an approach to this process.

History taking

Initially the approach to the patient should use *open-ended* questions aimed at eliciting a full description of the pain and its associated features. Useful questions include:

'Can you describe your pain for me in more detail?'
'Please tell me everything you can about the pain you have and anything you think might be associated with it.'
'Please tell me more about the pain you experience and how it affects you.'

Only following a full description of the pain by the patient should the history taker ask closed questions designed to complete the picture.

In taking the history it is essential to elucidate the presence of warning or 'alarm' features (Box 1.1). These are indicators that increase the likelihood that an organic condition underlies the pain. The alarm features guide further investigation.

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Historical features that it is important to elicit include the following.

Onset

- **Gradual or sudden?** Pain of acute onset may result from an acute vascular event, obstruction of a viscus or infection. Pain resulting from chronic inflammatory processes and functional causes are more likely to be of gradual onset.

Frequency and duration

- **Colicky pain (which progresses and remits in a crescendo–decrescendo pattern)?** Usually related to a viscus (e.g. intestinal renal and biliary colic), whereas constant intermittent pain may relate to solid organs (Box 1.2).
- **How long has the pain been a problem?** Pain that has been present for weeks is unlikely to have an acutely threatening illness underlying it and pain of very longstanding duration is unlikely to be related to malignant pathology.

Location: radiation or referral (Figure 1.1)

- **Poorly localised?** Usually related to a viscus (e.g. intestinal, renal and biliary colic).
- **Located to epigastrium?** Disorders related to the liver, pancreas, stomach and proximal small bowel (from the embryological foregut).
- **Located centrally?** Disorders related to the small intestine and proximal colon (from the embryological midgut).

Box 1.1 Alarm features precluding a diagnosis of irritible bowel syndrome (IBS).

History
- Weight loss
- Older age
- Nocturnal wakening
- Family history of cancer or IBD

Examination
- Abnormal examination
- Fever

Investigations
- Positive faecal occult blood
- Anaemia
- Leucocytosis
- Elevated ESR or CRP
- Abnormal biochemistry

Box 1.2 Characteristic causes of different patterns of abdominal pain.

Chronic intermittent pain
- Mechanical:
  - Intermittent intestinal obstruction (hernia, intussusception, adhesions, volvulus)
  - Gallstones
  - Ampullary stenosis
- Inflammatory:
  - Inflammatory bowel disease
  - Endometriosis/endometritis
  - Acute relapsing pancreatitis
  - Familial Mediterranean fever
- Neurological and metabolic:
  - Porphyria
  - Abdominal epilepsy
  - Diabetic radiculopathy
  - Nerve root compression or entrapment
  - Uraemia
- Miscellaneous:
  - Irritable bowel syndrome
  - Non-ulcer dyspepsia
  - Chronic mesenteric ischaemia

Chronic constant pain
- Malignancy (primary or metastatic)
- Abscess
- Chronic pancreatitis
- Psychiatric (depression, somatoform disorder)
- Functional abdominal pain

- **Located to suprapubic area?** Disorders related to the colon, renal tract and female reproductive organs (from the embryological hindgut).

Radiation of pain may be useful in localising the origin of the pain. For example, renal colic commonly radiates from the flank to the groin and pancreatic pain through to the back.

Referred pain occurs as a result of visceral afferent neurons converging with somatic afferent neurons in the spinal cord and sharing second-order neurons. The brain then interprets the transmitted pain signal to be somatic in nature and localises it to the origin of the somatic afferent, distant from the visceral source.

Character and nature

- **Dull, crampy, burning or gnawing?** Visceral pain: related to internal organs and the visceral peritoneum.
- **Sharp, pricking?** Somatic pain: originates from the abdominal wall or parietal peritoneum (Figure 1.1).

One process can cause both features, the classical example being appendicitis which starts with a poorly localised central abdominal aching visceral pain; as the appendix becomes more inflamed and irritates the parietal peritoneum, it progresses to sharp somatic-type pain localised to the right lower quadrant.

Exacerbating and relieving features

Patients should be asked if there are any factors that 'bring the pain on or make it worse' and conversely 'make the pain better'. Specifically:

- **Any dietary features, including particular foods or the timing of meals?** Patients with chronic abdominal pain frequently attempt dietary manipulation to treat the pain. Pain consistently developing soon after a meal, particularly when associated with upper abdominal bloating and nausea or vomiting, may indicate gastric or small intestinal pathology or sensitivity.

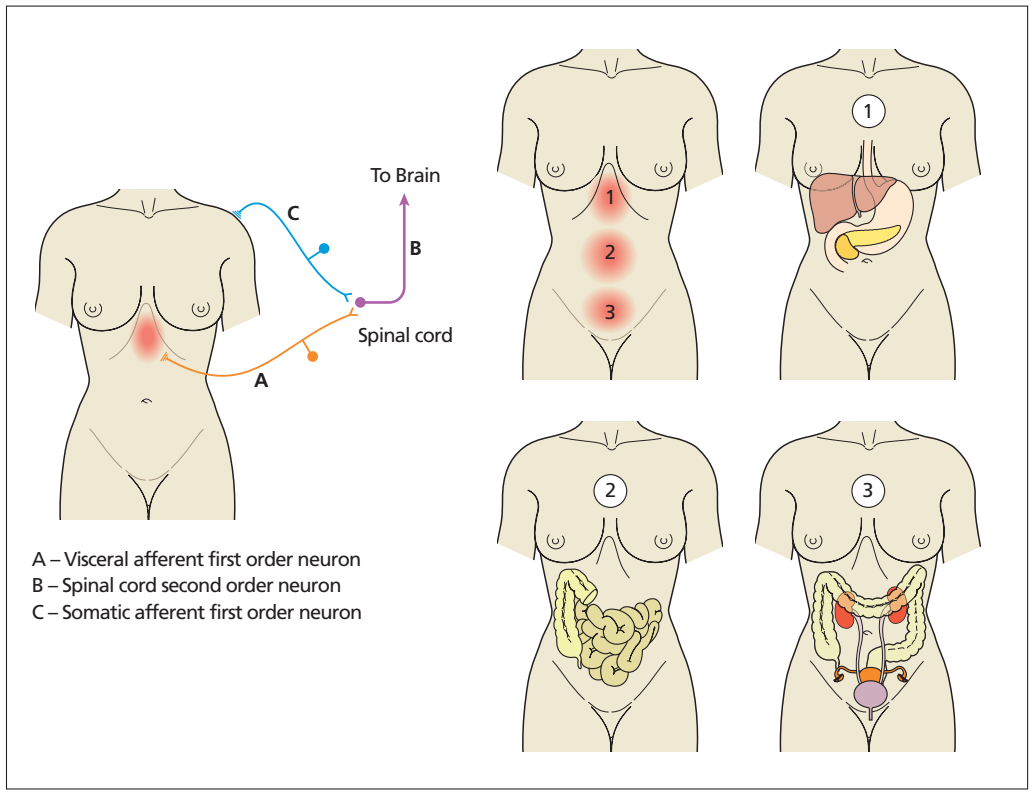

Figure 1.1 Location of pain in relation to organic pathology. A, Visceral afferent first-order neuron; B, spinal cord second-order neuron; C, somatic afferent first-order neuron.

- **Relief of low abdominal pain by the passage of flatus or stool?** This indicates rectal pathology or increased rectal sensitivity.
- **The effect of different forms of analgesia or antispasmodic used may give clues as to the aetiology of the pain.** Simple analgesics such as paracetamol may be more effective in treating musculoskeletal or solid organ pain, whereas antispasmodics such as hyoscine butylbromide (Buscopan) or mebeverine may be more beneficial in treating pain related to hollow organs.
- **Pain associated with twisting or bending?** More likely related to the abdominal wall than intra-abdominal structures.
- **Pain severity** may be affected by stress in functional disorders, but increasing evidence shows that psychological stress also plays a role in the mediation of organic disease, such as inflammatory bowel disease (IBD).

Any associated symptoms?

The presence of associated symptoms may be instrumental in localising the origin of the pain.

- **Relationship to bowel habit: frequency, consistency, urgency, blood, mucus and any association of changes in the bowel habit with the pain is important.** Fluctuation in the pain associated with changes in bowel habit is indicative of a colonic process and is typical of irritable bowel syndrome (IBS).
- **Vomiting or upper abdominal distension?** Suggestive of small bowel obstruction or ileus.
- **Haematuria?** Indicates renal colic.
- **Palpable lump in the area of tenderness?** Suggests an inflammatory mass related to transmural inflammation of a viscus, but may simply be related to colonic loading of faeces.

Examination technique

The physical examination begins with a careful **general inspection**.

- **Does the patient look unwell?** Obvious weight loss or cachexia is an indicator of malabsorption or undernourishment.
- **Is the patient comfortable? If in acute pain, are they adopting a position to ease the pain?** The patient lying stock still in bed with obvious severe pain may well have peritonitis, whereas a patient moving about the bed, unable to get comfortable, is more likely to have visceral pain such as obstruction of a viscus.
- **Observation of the skin** may demonstrate jaundice, pallor associated with anaemia, erythema ab igne (reticular erythematous hyperpigmentation caused by repeated skin exposure to moderate heat used to relieve pain), or specific extraintestinal manifestations of disease (Table 1.1). Leg swelling may be an indicator of decreased blood albumin related to liver disease or malnutrition.
- **Observe the abdomen** for visible abdominal distension (caused by either ascites or distension of viscus by gas or fluid).
- **Vital signs, including the temperature**, should be noted.
- **Examination of the hands** may reveal clues to intra-abdominal disease. Clubbing may be related to chronic liver disease, IBD or other extra-abdominal disease with intra-abdominal consequences. Pale palmar creases may be associated with anaemia. Palmar erythema, asterixis, Dupytren's contractures and spider naevi on the arms may be seen in chronic liver disease.
- **Inspection of the face** may reveal conjunctival pallor in anaemia, scleral yellow in jaundice, periorbital arcus senilis indicating hypercholesterolaemia and an increased risk of vascular disease or pancreatitis.
- **Careful cardiac and respiratory examinations** may reveal abnormalities associated with intra-abdominal disease. For example, peripheral vascular disease may indicate a patient is at risk for intestinal ischaemia; congestive heart failure is associated with congestion of the liver, the production of ascites and gut oedema; and pain from cardiac ischaemia or pleuritis in lower lobe pneumonia may refer to the abdomen.
- **Examination of the GI system *per se* begins with careful inspection of the mouth with the aid of**

Table 1.1 Extraintestinal manifestations of hepatogastrointestinal diseases.

Disease	Dermatological	Musculoskeletal
Inflammatory bowel disease:		
• Crohn's disease	Erythema nodosum, pyoderma gangrenosum	Axial arthritis more common
• Ulcerative colitis	Erythema nodosum, pyoderma gangrenosum	Axial and peripheral arthritis similar in frequency
Enteric infections (Shigella, Salmonella, Yersinia, Campylobacter)	Keratoderma blennorrhagica	Reactive arthritis
Malabsorption syndromes:		
• Coeliac sprue	Dermatitis herpetiformis	Polyarthralgia
Viral hepatitis:		
• Hepatitis B	Jaundice (hepatitis), livedo reticularis, skin ulcers (vasculitis)	Prodrome that includes arthralgias; mononeuritis multiplex
• Hepatitis C	Jaundice (hepatitis), palpable purpura	Can develop positive rheumatoid factor
Henoch–Schönlein purpura	Palpable purpura over buttocks and lower extremities	Arthralgias

a torch and tongue depressor. The presence of numerous or large mouth ulcers or marked swelling of the lips may be associated with IBD. Angular stomatitis occurs in iron deficiency. Glossitis may develop in association with vitamin B_{12} deficiency caused by malabsorption.

- **Examination of the thyroid is followed by examination of the neck and axilla** for lymphadenophathy.
- **Careful inspection of the abdomen is repeated and the abdominal examination is completed as described in Part IV, taking great care to avoid causing undue additional discomfort**. The examiner must be careful to first ask if there are any tender spots in the abdomen before laying on a hand. Special care should be taken, starting with very light palpation, asking the patient to advise the examiner of any discomfort felt and by watching the patient's expression at all times. Only if light palpation is tolerated in an area of the abdomen should deep palpation be undertaken in that area. A useful additional sign to elicit when areas of localised tenderness are found is Carnett's sign. Whilst the examiner palpates over the area of tenderness, the patient is asked to raise their head from the bed against the resistance provided by the examiner's free hand on their forehead. If the palpation tenderness continues or intensifies during this manoeuvre, it is likely to be related to the abdominal wall rather than to intra-abdominal structures.

Anatomy and physiology of abdominal pain

Pain within the abdomen can be produced in two main ways: irritation of the parietal peritoneum or disturbance of the function and/or structure of the viscera (Box 1.3). The latter is mediated by autonomic innervation to the organs, which respond primarily to distension and muscular contraction. The resulting pain is dull and vague. In contrast, chemical, infectious or other irritation of the parietal peritoneum results in a more localised, usually sharp or burning pain. The location of the pain correlates more closely with the location of the pathology and may give important clues as to the diagnosis. However, once peritonitis develops, the pain becomes generalised and the abdomen typically becomes rigid (guarding).

Box 1.3 Character of visceral versus somatic pain.

Visceral

- Originates from internal organs and visceral peritoneum
- Results from stretching, inflammation or ischaemia
- Described as dull, crampy, burning or gnawing
- Poorly localised

Somatic

- Originates from the abdominal wall or parietal peritoneum
- Sharper and more localised

Referred pain occurs due to convergence of visceral afferent and somatic afferent neurons in the spinal cord. Examples include right scapula pain related to gallbladder pain and left shoulder region from a ruptured spleen or pancreatitis.

Approach to differential diagnosis of pain and directed investigation

Following a careful history and examination, the clinician should be able to develop an idea of which organ(s) are likely to be involved and what the likely pathogenesis might be considering the demographics of the patient and the nature of the pain. It is important to list the most likely diagnoses based on these factors first. The differential can then be expanded by the application of a surgical sieve (as described in Part IV) to add the less likely possibilities.

Most patients should have a minimal blood panel to rule out warning features and to make any obvious diagnoses. These would include FBC; urea, creatinine and electrolytes; LFTs; and coeliac antibodies, especially if there is any alteration of bowel habit. Further testing should be directed at each of the most likely diagnoses in the list of differential diagnoses. The clinician should attempt to choose the range of investigations that will most cost-effectively examine for the greatest number of likely diagnoses with the greatest sensitivity and specificity (see clinical example).

CLINICAL EXAMPLE

Clinical Picture Ms AP is a 37-year-old woman who describes 1 year of intermittent right lower quadrant abdominal pain. She is caucasian, her body mass index is 19 kg/m^2 and she is smokes 20 cigarettes/day. The pain first came on following an illness associated with vomiting and diarrhoea. She saw her GP and was given antibiotics but stool culture revealed no pathogens. The diarrhoea settled spontaneously and she currently opens her bowels three times a day to soft-to-loose stool with no blood or mucous. The pain is aching and intermittent but seems to be worse during periods of life stress. It often occurs about half an hour after meals and is associated with abdominal bloating and on occasion nausea, but no vomiting. It lasts 30 min to some hours at a time. There is no position in which she can get comfortable with the pain and she describes herself as "writhing around" with the pain. She has reduced the size of her meals and avoids excess fibre, which seems to help. No specific foods contribute to the symptoms. Opening her bowels does not relieve the pain. She has trialled no medications. She has lost 5 kg in weight in the last year. The pain does not wake her at night and there is no nocturnal diarrhoea. There has been no change in the menstrual cycle and no association of the pain with menses. There has been no haematuria and she has never passed stones with the urine. She is on no regular medication. There is no significant family history.

Observation reveals a thin woman with no hand or face signs of gastrointesintal disease; in particular, no pallor, skin lesions, angular stomatitis, mouth ulceration or tongue swelling. The abdomen is not distended. There is localised tenderness in the right lower quadrant. No mass is palpable. Carnett's sign is negative (the tenderness disappears when the patient lifts her head from the bed). There is no organomegaly. Bowel sounds are normal.

Synthesis (see Table 1.2) In considering the differential diagnosis, one must first consider which organ(s) might be involved. The central and aching nature of the pain, as well as the fact that it causes the patient to writhe around, suggest that it is originating in a hollow organ, perhaps the small bowel or proximal colon. The localised tenderness further localises the pain to the distal small bowel or proximal colon. The onset was associated with a probable gastroenteritis and the bowel habit is mildly disturbed, also suggesting an intestinal cause. The lack of association with menses and the absence of other urinary symptoms make conditions of the reproductive system and renal tract less likely.

The most likely diagnoses in this setting are IBS and functional GI disease. Use of a surgical sieve applied to the distal small bowel and proximal colon expands the list to include infection, neoplasia including benign neoplasia resulting in intermittent intussusceptions, and, unlikely in a young woman, intestinal ischaemia. Less likely causes in other organ systems include biliary colic, ovarian pain and renal colic.

Initial investigation reveals a microcytic anaemia but no abnormality of the renal and liver tests and negative coeliac antibodies. Stool culture and examination for ova, cysts and parasites are negative. Urine dipstick shows no blood. Warning features in the form of weight loss and anaemia prompt further investigation. The investigation of choice to rule out inflammatory disease in the terminal ileum and colon is ileocolonoscopy and biopsy. The standard investigation for the remaining small bowel is CT (or MRI) enterography. This will also effectively investigate for biliary disease, ovarian disease and renal disease. More expensive and invasive investigations designed to examine for the less likely diagnoses are not utilised in the first instance (see Chapter 6).

At colonoscopy the caecum and terminal ileum are seen to be inflamed and ulcerated. Biopsies show chronic inflammation, ulceration and granuloma formation suggestive of Crohn's disease. CT shows no disease of the ovaries, kidneys or biliary tree but does suggest thickening and inflammation of the terminal ileum and caecum. There is no significant lymphadenopathy. A diagnosis of probable Crohn's disease is made and the patient treated accordingly.

Table 1.2 Approach to differential diagnosis and directed investigation.

Likely organ involved	Likely pathology	Investigation choices	Investigation plan
Small bowel and colon	Inflammatory bowel disease	Ileocolonoscopy CT enterography US small bowel MRI	
	Irritable bowel syndrome	Suggestive symptom complex in the absence of other diagnoses	
	Infection	Stool culture and examination for C. difficile, ova, cysts and parasites Specific parasitic serology if peripheral eosinophilia	Stool test Ileocolonoscopy CT (or MRI) enterography
	Neoplasia	Ileocolonoscopy and small bowel follow-through	
	Ischaemia	Angiography	
Biliary system	Biliary stones, neoplasia	Ultrasound abdomen MRCP ERCP	
Ovary	Ovarian cyst, torted ovary	Ultrasound pelvis CT pelvis	
Renal	Renal stones	Ultrasound abdomen CT urogram	

US, ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography scan.

Acute abdominal pain

The patient presenting with acute abdominal pain presents a particular challenge to the clinician. Pain production within the abdomen is such that a wide range of diagnoses can present in an identical manner. However, a thorough history and examination still provides the cornerstone of assessment. It is essential to have an understanding of the mechanisms of pain generation. Equally, it is important to recognise the alarm symptoms and initial investigative findings that help to determine which patients may have a serious underlying disease process, and therefore warrant more expeditious evaluation and treatment.

History taking

The assessment of the patient with abdominal pain proceeds in the same way whatever the severity of the pain; however, in the acute setting, assessment and management may need to proceed simultaneously and almost invariably involve consultation with a surgeon. Much debate has centred on the pros and cons of opiate analgesia in patients with severe abdominal pain, as this may affect assessment. Current consensus is that while judicious use of opiate analgesia may affect the examination findings, it does not adversely affect the outcome for the patient and is preferable to leaving a patient in severe pain.

The history (Table 1.3) gives vital clues as to the diagnosis and should include questions regarding the location (Figure 1.2), character, onset and severity of the pain, any radiation or referral, any past history of similar pain, and any associated symptoms.

Careful exclusion of past or chronic health problems that may have progressed to, or be associated with, the current condition is important. A patient with chronic dyspepsia may now be

Table 1.3 Historical features in acute abdominal pain examination.

Where is the pain?	See Figure 1.2
Character of the pain?	Acute waves of sharp constricting pain that 'takes the breath away' (renal or biliary colic) Waves of dull pain with vomiting (intestinal obstruction) Colicky pain that becomes steady (appendicitis, strangulating intestinal obstruction, mesenteric ischaemia) Sharp, constant pain, worsened by movement (peritonitis) Tearing pain (dissecting aneurysm) Dull ache (appendicitis, diverticulitis, pyelonephritis)
Past similar pain?	"Yes" suggests recurrent problems such as ulcer disease, gallstone colic, diverticulitis or mittelschmerz
Onset?	Sudden: 'like a thunderclap' (perforated ulcer, renal stone, ruptured ectopic pregnancy, torsion of ovary or testis, some ruptured aneurysms) Less sudden: most other causes
Severity of the pain?	Severe pain (perforated viscus, kidney stone, peritonitis, pancreatitis) Pain out of proportion to physical findings (mesenteric ischaemia)
Radiation/referral?	Right scapula (gallbladder pain) Left shoulder region (ruptured spleen, pancreatitis) Pubis or vagina (renal pain) Back (ruptured aortic aneurysm)
Relieving factors?	Antacids (peptic ulcer disease) Lying as quietly as possible (peritonitis)
Associated symptoms?	Vomiting precedes pain and is followed by diarrhoea (gastroenteritis) Delayed vomiting, absent bowel movement and flatus (acute intestinal obstruction; the delay increases with a lower site of obstruction) Severe vomiting precedes intense epigastric, left chest or shoulder pain (emetic perforation of the intra-abdominal oesophagus)

presenting with perforation of a duodenal ulcer. The patient with severe peripheral vascular disease, or who has had recent vascular intervention, might have acute mesenteric ischaemia. A binge drinker with past episodes of alcohol-related pain is at risk for acute pancreatitis, as is the patient with known cholelithiasis. Patients with past multiple abdominal surgeries are at risk for intestinal obstruction.

Questioning regarding current and past prescribed, illicit and complementary medicine use is necessary. The patient using NSAIDs is at risk of peptic ulceration; use of anticoagulants increases the risk of haemorrhagic conditions; prednisone or immunosuppressants may blunt the inflammatory response to perforation or peritonitis resulting in less pain than expected.

Examination

Initial assessment is aimed at determining the seriousness of the illness. A happy, comfortable-appearing patient rarely has a serious problem, unlike one who is anxious, pale, sweaty or in obvious pain. Vital signs, state of consciousness and other signs of peripheral perfusion must be evaluated.

- **Examination of the non-abdominal organ systems** is aimed at determining any evidence for an extra-abdominal cause for the pain:
  - Abdominal wall tenderness and swelling with rectus muscle haematoma . Extremely tender, sometimes red and swollen scrotum with testicular torsion;
  - Resolving (sometimes completely resolved) rash in post-herpetic pain;
  - Ketones on the breath in diabetic ketoacidosis;
  - Pulmonary findings in pneumonia and pleuritis.
- **Examination of the abdomen** focuses on the detection of peritonitis, any intra-abdominal masses or organomegaly, and localisation of the underlying pathology:
  - Distension of the abdomen may be associated with intestinal obstruction;

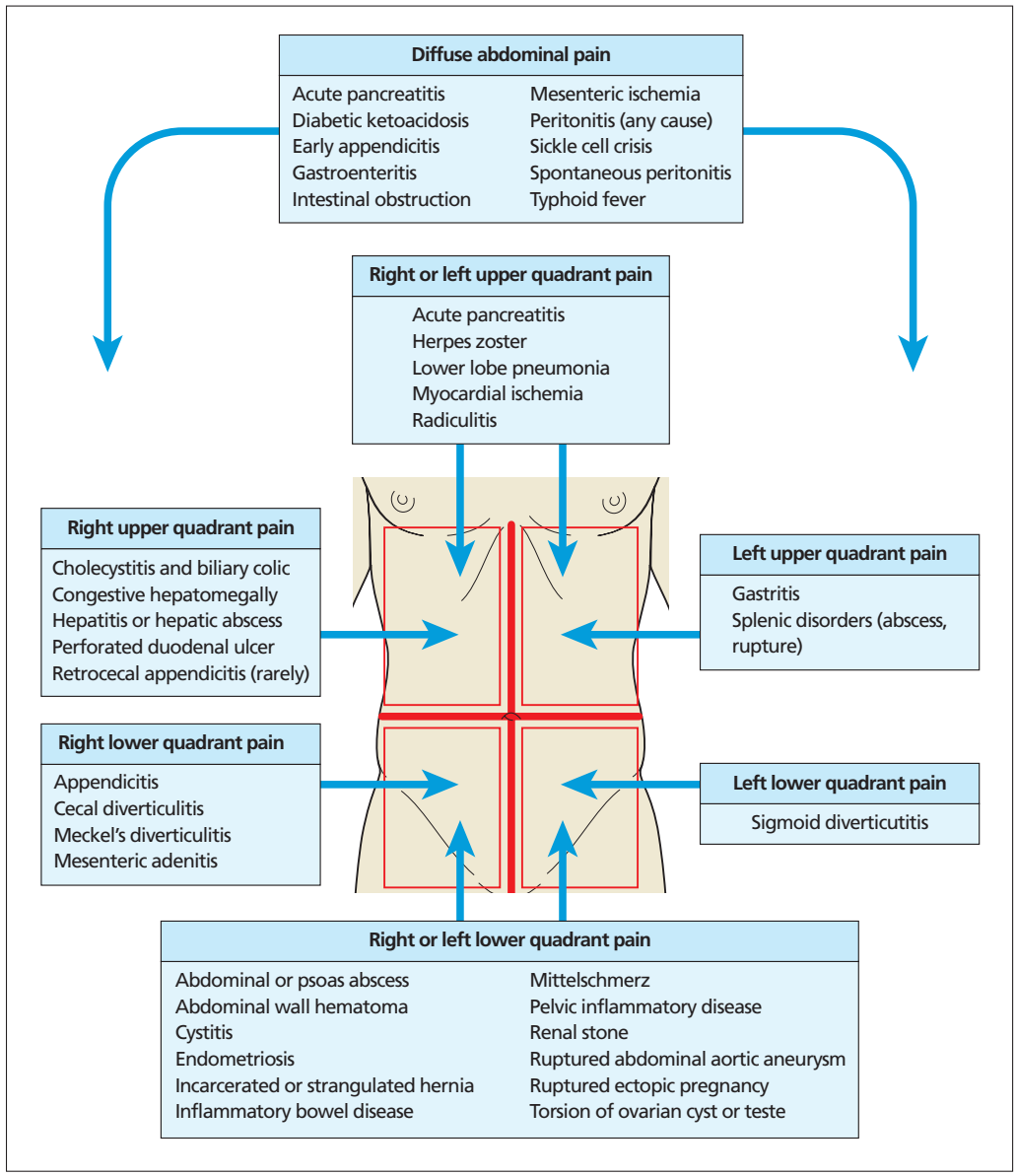

Figure 1.2 Likely pathologies according to location of acute pain.

- Bruising at the flanks (Grey Turner's sign) and periumbilically (Cullen's sign) is occasionally seen in acute haemorrhagic pancreatitis;
- Absent bowel sounds is indicative of ileus and in the presence of severe pain suggests peritonitis;
- High-pitched or over-active bowel sounds might indicate intestinal obstruction.

- **Palpation** should start with very light examination well away from the area of greatest pain. Guarding, rigidity and rebound indicate peritoneal irritation. Guarding is a slow and sustained involuntary contraction of the abdominal muscles, rather than the flinching that is observed with sensitive or anxious patients. Careful exclusion of hernias at the inguinal canals and over surgical scars,

as well as pelvic and rectal examination, is essential.

Investigations

Most patients will have a FBC, urea, creatinine and electrolytes, and dipstick urinalysis performed, although the results from these tests are neither sensitive nor specific. Serum lipase, however, is useful in detecting acute pancreatitis. It is essential that erect chest and abdomen, and supine abdominal X-rays are performed when there is the possibility of intestinal perforation or obstruction. If the patient cannot sit up, the left lateral position may be used.

Modern imaging can detect the underlying pathology in acute abdominal pain with high sensitivity and specificity. While ultrasound examination has the benefits of portability and avoidance of radiation exposure, it is most useful in detecting disease of the gallbladder, and gynaecological and obstetric conditions. CT has emerged as the dominant imaging tool for evaluation of the patient with severe acute abdomen. This has come about with the frequent advent of easy access to helical CT within or adjacent to the emergency department. The proper execution and interpretation of CT in this setting has been shown to reduce the need for exploratory laparotomy and hence morbidity, mortality and medical expense.

2

Approach to the patient with liver disease

Patients with liver disease can present with a wide range of complaints, and the clinician must remain alert at all times to the possibility of hepatic involvement in disease. Increasingly commonly, asymptomatic patients will present because of liver test abnormalities discovered incidentally. Once the presence of hepatic dysfunction has been established, the not always straightforward task of defining the underlying pathology is critical to planning appropriate management.

History taking

Liver disease can present in a variety of ways:

- **Non-specific symptoms** include fatigue, anorexia, nausea and, occasionally, vomiting;
- **Loose, fatty stools (steatorrhoea)** can occur if cholestasis interrupts bile flow to the small intestine;
- **Fever (due to liver pyrogens)** may be the first feature in viral or alcoholic hepatitis;
- **Jaundice** becomes visible when the serum bilirubin reaches 34–43 µmol/l (2–2.5 mg/dl). While jaundice may be related to hepatic dysfunction, equally it can be a result of bilirubin overproduction. Mild jaundice without dark urine suggests unconjugated hyperbilirubinaemia (most often caused by haemolysis or Gilbert's syndrome).

The historical features that it is important to elicit include the following.

Onset and duration

- **Did the symptoms come on gradually or suddenly? How long have the symptoms been a problem?** Symptoms of acute onset may result from an acute vascular event, toxic cause, obstruction of the biliary system or acute infection. Symptoms resulting from chronic inflammatory processes are more likely to be of gradual onset. The development of dark urine (bilirubinuria) due to increased serum bilirubin, from hepatocellular or cholestatic causes, often precedes the onset of visible jaundice.
- **Identify precipitating events** related to the onset of the symptoms; direct questions often need to be asked regarding exposure to common causes (Box 2.1), in particular:
  - Any association with pain that might relate to biliary obstruction?
  - Any use of medicines – prescribed, complementary or illicit?
  - Any trauma or major stress including surgery?
  - Any association with starvation (important in Gilbert's syndrome; see Chapter 20)?
  - Any history of marked weight loss or gain?
  - Any association with vascular events or hypotension?
  - Any possible infectious contact or exposure?

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Box 2.1 Common causes of liver disease.

Infectious liver disease
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Epstein–Barr virus

Drug-induced hepatitis or cholestasis

Vascular disease
- Ischaemic hepatitis
- Portal vein thrombosis
- Budd–Chiari syndrome
- Nodular regenerative hyperplasia
- Veno-occlusive disease of the liver

Immune hepatitis
- Autoimmune hepatitis
- Granulomatous hepatitis

Deposition diseases
- Wilson's disease
- Haemochromatosis
- Alpha-1-antitrypsin deficiency

Alcoholic liver disease

Fatty liver
- Non-alcoholic fatty liver disease
- Non-alcoholic steatohepatitis
- Focal fatty liver

Tumours and lesions of the liver
- Hepatocellular carcinoma
- Liver secondaries
- Hepatic adenoma
- Focal nodular hyperplasia of the liver
- Hepatic cyst/polycystic liver disease
- Hepatic haemangioma

Congenital liver disease
- Congenital hepatic fibrosis
- Gilbert's syndrome
- Dubin–Johnson syndrome
- Crigler–Najjar syndrome

Liver disease of pregnancy
- Hyperemesis gravidarum
- Cholestasis of pregnancy
- Acute fatty liver of pregnancy
- HELLP syndrome

Cryptogenic cirrhosis

Perpetuating and exacerbating features

Patients should be asked if there are any factors that 'bring on or make the symptoms worse or better'. Pain of a colicky nature that is exacerbated by eating, in particular fatty meals, may indicate a biliary cause for jaundice. A relapsing and remitting course associated with any toxic or medicinal exposure must be carefully sought. The use of immunosuppressive medications for other conditions may improve chronic inflammatory conditions, but conversely may exacerbate infectious causes.

Associated symptoms

The presence of associated symptoms can help localise the origin of symptoms:

- Onset of nausea and vomiting prior to jaundice is associated with acute hepatitis or common bile duct obstruction by a stone;
- Presence of pale stool, bilirubinuria and generalised pruritis is indicative of cholestasis. If this is associated with fevers and rigors, an extrahepatic cause is more likely;
- Central abdominal pain radiating to the back might indicate a pancreatic cause for obstruction;
- Gradual onset of anorexia and malaise commonly occurs in alcoholic liver disease, chronic hepatitis and cancer;
- Disturbances of consciousness, personality changes, intellectual deterioration and changes in speech might indicate hepatic encephalopathy.

Past medical and family history

The importance of a thorough past medical history, social history, family history and list of medicines, including complementary treatments, cannot be stressed enough in the evaluation of liver disease.

- Any history of vascular disease, in particular thromboembolic disease, might point to a vascular cause for hepatic dysfunction.
- Previous or concomitant autoimmune disease increases the possibility of autoimmune hepatitis.
- Pregnancy is associated with a particular set of hepatic problems.
- Past carcinoma raises the concern of metastatic liver disease.
- A history of obesity, in particular in association with other features of the metabolic syndrome, increases the risk of steatohepatitis.
- Patients should be carefully questioned regarding the presence of liver disease in the family. Inheritable liver conditions uncommonly present in adulthood but haemochromatosis and Wilson's disease should be considered. Hepatitis viruses, in particular hepatitis B, may be contracted congenitally. The metabolic syndrome shows a familial tendency and increases the risk of fatty liver disease.

Lifestyle history

- A careful alcohol history, past and present, is essential when interviewing the patient with liver disease.
- Risk factors for infectious hepatitis also need to be carefully questioned in all patients (intravenous drug use, transfusion history including blood products, and close contacts with hepatitis).
- The occupational history may reveal exposure to hepatotoxins (employment involving alcohol, but also carbon tetrachloride, benzene derivatives and toluene).
- A complete list of exposure to medicines, prescribed and illicit, conventional and complementary, must be sought. It must be remembered that in drug-induced liver disease the temporal association may appear obscure as the interval between exposure and development of symptomatic disease is variable (usually within 5–90 days).

Mental status assessment

It is important to document the mental state of all patients with known hepatic dysfunction, in particular cirrhosis. The Glasgow Coma Scale should be completed (Table 2.1) as it gives prognostically useful information. In the absence of disturbances of consciousness, early encephalopathy interferes with visual spatial awareness, demonstrated as a constructional apraxia, elicited by asking the patient to reproduce simple designs, most commonly a five-pointed star, or deterioration in the quality of handwriting.

Examination technique

The physical examination begins with a careful general inspection – the importance of observing for the stigmata of chronic liver disease (Table 2.2) relates to making the diagnosis (**C**ondition), and identifying aetiology (**C**ause) and decompensation (**C**omplications).

Table 2.1 Glasgow Coma Scale.

	6	5	4	3	2	1
Eyes	N/A	N/A	Opens eyes spontaneously	Opens eyes in response to voice	Opens eyes in response to painful stimuli	Does not open eyes
Verbal	N/A	Oriented, converses normally	Confused, disoriented	Utters inappropriate words	Incomprehensible sounds	Makes no sounds
Motor	Obeys Commands	Localises painful stimuli	Withdraws from painful stimuli	Abnormal flexion to painful stimuli	Extension to painful stimuli	Makes no movements

Table 2.2 Stigmata of chronic liver disease (progressing through the hands, face, abdomen and legs).

Diagnosis	Aetiology	Decompensation
Palmar erythema	Dupuytren's contracture (alcohol)	Leuconychia (synthetic function)
Clubbing	Skin discoloration (haemachromatosis)	Multiple bruises (synthetic function)
Excoriation	Tattoos (viral hepatitis)	Asterixis (encephalopathy)
Spider naevi (in distribution of superior vena cava)	Peripheral neuropathy (alcohol)	Drowsiness (encephalopathy)
Conjunctival pallor (anaemia)	Kayser–Fleisher rings (Wilson's)	Jaundice (excretory function)
Gynaecomastia	Parotidomegaly (alcohol)	Hyperventilation (encephalopathy and acidosis)
Female pattern body hair	Cerebellar signs: nystagmus, intention tremor (alcohol and Wilson's)	Ascites (portal hypertension and synthetic function)
Caput medusa (recanalised umbilical vein)	Chronic pulmonary disease (α-1-antitrypsin deficiency, cystic fibrosis)	Pedal/sacral oedema (synthetic function and right heart failure)
Distended abdominal veins	Obesity (NAFLD)	
Testicular atrophy	Diffuse lymphadenopahy (lymphoproliferative disease)	

- **Careful inspection of the abdomen is repeated and the abdominal examination is completed as described in Part IV.** Particular care should be taken to define the liver edges by percussion, and the position, texture and consistency of the lower liver edge by palpation. The normal liver span is less than 12.5 cm. The normal liver edge may be pushed down by pulmonary hyperinflation in emphysema or asthma and with a Riedel's lobe, which is a tongue-like projection from the right lobe's inferior surface. Not all diseased livers are enlarged; a small liver is common in cirrhosis. Cachexia and an unusually hard or lumpy liver more often indicates metastases than cirrhosis. A tender liver suggests hepatitis, hepatocellular cancer or hepatic abscess, but may occur with rapid liver enlargement, e.g. in right heart failure (Table 2.3).
- **Careful examination for the spleen is essential**. While enlargement of the spleen and liver might suggest chronic liver disease with portal hypertension, hepatosplenomegaly without other signs of chronic liver disease may be caused by an infiltrative disorder (e.g. lymphoma, amyloidosis or, in endemic areas, schistosomiasis or malaria), although jaundice is usually minimal or absent in such disorders.
- **Shifting dullness** is elicited by demonstrating flank dullness to percussion that moves with repositioning of the patient. Very rarely it is possible for intra-abdominal cystic masses to cause 'pseudo-ascites'; hence if shifting dullness is found, it should be confirmed bilaterally to ensure it is due to ascitic fluid shift.

Approach to investigation and differential diagnosis

Following a careful history and examination, the likely pathological processes relevant to the patient should be identifiable. The most likely diagnoses should be listed first and this can then be expanded by the application of a surgical sieve (as described in Part IV).

All patients should have routine biochemistry, haematology and coagulation tests performed. Serial liver enzyme assays give a picture of the course of the illness. In **hepatitis** an initial diagnostic serological screen should examine for the commoner causes. This would commonly include:

- Hepatitis A, B and C serology;
- Autoimmune screen to include antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), smooth muscle antibodies

Table 2.3 Differential diagnosis based on features of the liver examination.

Diagnosis	Characteristics of the liver edge	Degree of hepatomegaly
Metastases	Irregular	Mild to massive
Fatty infiltration due to alcoholic liver disease, myeloproliferative disease	Smooth	
Right heart failure	Smooth Tender if rapid liver enlargement Pulsatile in tricuspid regurgitation	
Hepatocellular cancer	Smooth, tender and occasionally pulsatile	
Haemochromatosis, haematological disease (e.g. chronic leukaemia, lymphoma), fatty liver, infiltration (e.g. amyloid), granuloma (e.g. sarcoid)	Smooth	Mild to moderate
Hepatitis	Smooth and tender	Mild
Biliary obstruction	Smooth	
Hydatid disease, cysts	Firm and irregular	
Hepatic abscess	Smooth and tender	None to mild
Vascular abnormalities	May be smooth or irregular, may be pulsatile	
Cirrhosis from any cause	Firm and irregular	Small liver to mild hepatomegaly

(SMA) and liver/kidney microsomal antibody type 1 in the younger patient;
- Serum immunoglobulin levels are also commonly performed: there is some diagnostic sensitivity for elevated IgA in alcoholic liver disease and IgM in primary biliary cirrhosis;
- As reports of occult coeliac disease as a cause of LFT abnormalities are increasing, testing for antiendomysial (EMA) or antitissue transglutaminase (tTG) may be beneficial, particularly in the patient with GI disturbance;
- Fasting blood sugars and lipids should be tested where fatty liver disease is suspected;
- In the young patient the rare genetic causes, Wilson's disease (serum caeruloplasmin), hereditary haemochromatosis (serum ferritin and transferrin saturation) and alpha-1-antitrypsin deficiency (AAT concentrations), can be screened for.

Investigation of the liver architecture and hepatic vasculature by ultrasound is generally indicated. Due to its low cost and the absence of ionising radiation, ultrasound can be considered the imaging modality of first choice. However, ultrasound may be difficult in the obese or gaseous patient, in those with a high-lying liver completely covered by the rib margin and in postoperative patients with dressings or painful scars. CT and MRI are useful second-line modalities and have largely replaced radioisotope scanning.

Liver biopsy is not usually required for the diagnosis of acute hepatitis. Its use is typically reserved for the assessment of chronic liver disease in order to inform prognosis and management, and following hepatic transplantation. Liver biopsy can, however, be useful in confirming deposition diseases of the liver and where a clear diagnosis as to the cause of hepatitis has not been forthcoming after a complete serological work-up. Biopsy of possible malignant tumours has to be weighed against the risk of tumour seeding (Box 2.2). Biopsy may be undertaken through percutaneous, transjugular or rarely laparoscopic approaches.

Assessment of the severity of liver disease

Where chronic liver disease is confirmed, some assessment of the severity of hepatic dysfunction

Table 2.4 Child–Pugh scoring system.

Measure	1 point	2 points	3 points
Bilirubin (total) (μmol/l [mg/dl])	<34 [<2]	34–50 [2–3]	>50 [>3]
Serum albumin	>35	28–35	<28
INR	<1.7	1.71–2.20	>2.20
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

Box 2.2 Indications for liver biopsy.

- Diagnose unexplained liver enzyme abnormalities
- Diagnose and assess alcoholic liver disease
- Diagnose and assess non-alcoholic steatosis
- Diagnose and stage chronic hepatitis (viral and autoimmune)
- Diagnose storage disorders (iron, copper)
- Diagnose hepatomegaly of unknown cause
- Diagnose unexplained intrahepatic cholestasis
- Monitor use of hepatotoxic drugs (e.g. methotrexate)
- Obtain histology of suspicious lesions
- Obtain histology or culture in systemic illnesses
- Following liver transplant: suspected rejection
- Pre-liver transplant to assess donor

should be made. The commonest scoring system used is the Child–Pugh score (Table 2.4). This score is calculated using the total bilirubin, serum albumin, INR, degree of ascites and grade of hepatic encephalopathy. Based on this score patients are grouped into three severity levels: A, B and C.

These Child–Pugh 'classes' are predictive of prognosis and useful in determining the required strength of treatment and the necessity of liver transplantation (Table 2.5). Another specialised pretransplantation assessment score is the Model for End-Stage Liver Disease (MELD) score (Table 2.6).

Table 2.5 Prognosis related to Child–Pugh scoring system.

Points	Class	1-year survival (%)	2-year survival (%)
5–6	A	100	85
7–9	B	81	57
10–15	C	45	35

Table 2.6 Model for End-Stage Liver Disease (MELD) score.

MELD score	3-Month mortality (% hospitalised patients)
≤9	4
10–19	27
20–29	76
30–39	83
≥40	100

3

Approach to the patient with luminal disease

This chapter provides both a basis to structure revision and a practical approach to patients presenting in gastroenterology wards and clinics. Abdominal pain is dealt with in Chapter 1. The other common presenting problem of GI bleeding is dealt with in Chapters 7 and 8.

Dysphagia

Dysphagia is defined as difficulty in swallowing, distinct from **odynophagia**, which means pain on swallowing. It also needs to be distinguished from **globus**, which is a functional syndrome of the sensation of a lump in the throat in the absence of an organic cause. In taking a history, one needs to differentiate one of three general causes – oropharyngeal or oesophageal mechanical or oesophageal dysmotility (Table 3.1).

History

See Table 3.1.

Investigation

- **Condition and cause**:
  - Endoscopy: first-choice investigation, allows biopsy and/or dilatation of strictures; may be performed after barium swallow to allow exclusion of pharyngeal pouch, which could be perforated by the unsuspecting endoscopist;
  - Barium swallow (irregular stricture = malignant; smooth stricture = benign);
  - Chest X-ray (hilar lymphadenopathy = oesophageal malignancy);
  - Videofluorsocopy (if oropharyngeal cause suspected);
  - ENT opinion (if oropharyngeal cause suspected);
  - Systemic sclerosis antibodies.
- **Complications**: FBC (anaemia = oesophageal malignancy, malnutrition, Plummer–Vinson syndrome);
  - LFTs (stage oesophageal malignancy).

Causes

See Table 3.2.

Management

Specific management depends on the underlying cause (see appropriate sections).

Nausea and vomiting

Vomiting is the violent expulsion of gastric and intestinal content induced by contraction of the abdominal musculature and diaphragm. It is distinct from **regurgitation**, which is the passive passage of gastric content without abdominal

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Anton Emmanuel and Stephen Inns.

Table 3.1 Historical features of help in identifying cause of dysphagia.

Clinical features	Oropharyngeal	Oesophageal mechanical cause	Oesophageal dysmotility cause
Initiating swallow	Difficult	Unaffected	Unaffected
Interval to dysphagia after swallow	Instant	Few seconds	Few seconds
Progression	Variable	Progressively worsening	Intermittent
Type of food	Liquids	Solids	Liquids and solids
Associated symptoms	Choking, nasal regurgitation, drooling	Weight loss, prior heartburn	Odynophagia
Associated signs	Cranial nerve signs	Cervical lymph nodes, anaemia	Systemic sclerosis?

Table 3.2 Causes of dysphagia, classified by frequency of occurrence.

	Oropharyngeal	Oesophageal
Common	Stroke Candidiasis Globus sensation	Benign (peptic) stricture Oesophageal carcinoma Oesophagitis
Less common	Pharyngeal pouch Motor neurone disease Xerostomia	Dysmotility (achalasia > spasm > systemic sclerosis) Webs and rings External pressure (hilar nodes, lung cancer)
Rare	Oral tumours Severe aphthous ulcers Muscular dystrophy	Oesophageal infections Retrosternal goitre Corrosive stricture

contraction; it may reflect oesophageal or gastric disease. **Nausea** is the perceptual component of vomiting.

History

- **Timing**: acute cases (see below) need to be distinguished from chronic, as causation is quite different:
  - If shortly after meals, suggests a gastric cause;
  - If long after meals, suggests distal intestinal cause;
  - If unrelated to meals, suggests non-GI cause;
  - If mostly on waking, suggests CNS cause.
- **Amount of vomitus**:
  - Large volumes suggest obstruction or gastric cause;
  - Small volumes suggest a functional problem.
- **Content of vomitus**:
  - If bile (bitter brown liquid) present, then pylorus is patent, and gastroparesis is unlikely;
  - If undigested food is present, many hours after being eaten, then gastric cause is likely.
- **Associated features**:
  - If isolated, almost always functional;
  - Drug history (see causes below);
  - Neurological symptoms (see causes below).
- **Assessment**:
  - Signs of dehydration (*complication*);
  - Signs of sepsis (*cause*);
  - Signs of visible peristalsis and hernia (*cause*);
  - Sucussion splash (*condition*);
  - Dental enamel erosions (*cause* – GORD or bulimia);
  - Neurological signs (*cause*).

Investigation

Needs to be focused by consideration of causes (see below).

Box 3.1 Causes of vomiting.

Gastrointestinal

- Functional disorders:
  - Functional dyspepsia syndromes
  - IBS
- Obstructive:
  - Achalasia:
  - Gastric outlet obstruction
    - Pyloric stenosis
    - Gastroparesis
  - Small bowel obstruction
- Organic luminal disease:
  - Peptic ulcers
  - Upper GI cancers
  - Gastroenteritis
- Organic hepato-pancreato-biliary disease:
  - Hepatitis: acute and chronic
  - Pancreatitis: acute and chronic
  - Cholecystitis: acute and chronic

Neurological

- Vestibular disorders
- Raised intracranial pressure
- Migraine
- Demyelinating disorders

Psychogenic

- Bulimia nervosa > anorexia nervosa
- Psychogenic vomiting
- Cyclical vomiting syndrome

Alcohol

Drugs: almost any, but especially:

- Opiates
- Antibiotics, especially erythromycin
- Chemotherapy agents
- NSAIDs
- Anticonvulsants

Metabolic

- Uraemia
- Diabetic ketoacidosis
- Addison's disease

Pregnancy

Causes

The potential list of causes is enormous, but can be classified as in Box 3.1. More than one cause is often present.

Treatment

This should, where possible, be directed at treating the underlying cause (as per Box 3.1). Symptomatic relief may be obtained from:

- **Centrally-acting antiemetics**:
  - Phenothiazines (prochlorperazine, haloperidol):
    - Antidopamine effect;
    - Best for neurological, drug-induced and metabolic nausea;
    - Side-effects: sedation, orthostatic hypotension.
  - 5-HT_3 antagonists (ondansetron):
    - Antihistamine effect at chemoreceptor trigger zone;
    - Best for drug-induced nausea;
    - Well-tolerated, but expensive.
  - 5-HT_1 antagonists (diphenhydramine):
    - Antihistamine effect at chemoreceptor trigger zone;
    - Best for neurological causes of nausea;
    - Well tolerated, but limited efficacy.
- **Peripherally-acting antiemetics** *:*
  - Prokinetic agents (domperidone, metoclopramide):
    - Best for GI causes of vomiting;
    - Side-effects: gynaecomastia, extrapyramidal effects.
  - Motilin analogues (erythromycin):
    - Especially useful in gastroparesis.
- **Centrally- and peripherally-acting agents**:
  - Steroids (dexamethasone);
  - Benzodiazepines (lorazepam).

Constipation

Constipation is defined in purely symptomatic terms (in contrast to diarrhoea, which is defined as stool weight >200 g). Implicit in this, is the fact that constipation is merely a symptom, not a diagnosis. Constipation is distinct from the **irritable**

bowel syndrome (IBS) in that abdominal pain is not necessarily associated with bowel dysfunction. It is defined as infrequent stools (<3 per week), passage of hard stools (>25% of the time), straining to empty the rectum (>25% of the time) or a sensation of incomplete evacuation (>25% of the time).

Constipation is one of the most common GI complaints. It affects about 25% of the population at some time, being more common in women and the elderly.

PHYSIOLOGY OF GUT TRANSIT

The time taken for food to travel through the whole gut (oroanal transit time) varies widely in the population, between 20 and 40 h. 80% of this time is spent in transit through the colon. There are two forms of contractions that occur in the colon, the segmental ones that encourage reabsorption of water and the less frequent propagated contractions that propel content downstream. The latter are complemented by the gastrocolic response, which describes the increase in segmental activity that occurs after eating. Fatty and carbohydrate meals enhance the response, which is dependent on vagal function. This response is a strong stimulus to colonic transit and defaecation and explains why constipation may result from an inadequate dietary habit.

Once stool is in the rectum, there needs to be co-ordination between the pelvic floor, abdominal musculature and anal sphincters in order to allow evacuation of rectal content.

Table 3.3 Secondary causes of constipation.

Primary pathology	Examples
Endocrine conditions	Hypothyroidism* Hyperparathyroidism Diabetes mellitus* Glucagonoma
Neurological conditions	Multiple sclerosis Autonomic neuropathy Parkinson's disease* Spinal injury*
Psychogenic conditions	Affective disorders* Eating disorders* Dementia or learning difficulty
Metabolic	Hypercalcaemia Uraemia Hypokalaemia Porphyria Amyloidosis Lead poisoning
Colonic	Stricture Tumour* Ischaemia Diverticular disease*
Anal	Fissure* Polyp Tumour
Physiological	Pregnancy* Old age*
Drugs (all of which lead to prolongation of transit)	Opiates Anticholinergics Anticonvulsants Tricyclic antidepressants Antacids (aluminium and calcium containing ones) NSAIDs Iron Antihypertensives

*, Most common.

Classification

Constipation can be classified as primary or secondary to other disorders, and it is often multifactorial. The distinction is important as it will direct management. The secondary causes are listed in Table 3.3.

Primary causes can be due to constipation with a colon of normal diameter or with a dilated colon, but this is an clinically important distinction to make, and can be assessed on abdominal X-ray or barium study.

Constipation with a colon of normal diameter

Patients who have constipation with a colon of normal diameter can be classified into three subgroups:

- **Normal transit constipation**. This is the commonest type of constipation. It is characterised by a normal rate of stool movement through the colon, but the patient feels constipated. It is usually secondary to

perceived difficulty with defaecation and hard stools. Symptoms may overlap with those of constipation-predominant IBS since pain and bloating is common.

- **Slow transit constipation**. Most common in young women, with symptoms dating back to childhood. Characterised by infrequent bowel movements and slow movement of stool through the colon. Bloating, abdominal pain and an infrequent urge to defaecate are commonly associated with this condition. There may be underlying neural changes in the colon, though these may be secondary to the condition itself.
- **Disordered defaecation**. Usually due to dysfunction of the pelvic floor or anal sphincters. Patients typically report an inability to defaecate despite feeling an urge to do so, and need to use digital manipulation per vagina or per anum. Most often there is inco-ordination of the pelvic floor and anal sphincters resulting in non-propulsion of stool from the rectum; this may have been triggered by deliberately suppressing the urge to defaecate. Alternatively there may be structural abnormalities, such as a rectocoele (a bulging of the rectum into the posterior wall of the vagina) or rectal intussusception (telescoping of the rectum into itself during straining), which cause an 'obstruction' to defaecation.

Constipation with a dilated colon

Severe constipation with gut dilatation is secondary to neuromuscular disorders of the colon:

- Hirschsprung's disease (see p. 108);
- Idiopathic megacolon (see p. 108);
- Chronic intestinal pseudo-obstruction (see p. 92).

History

- **Stool frequency and consistency**: hard stools suggest delayed transit; normal stools suggest normal transit; loose stools may relate to laxative use.
- **Need to strain or digitally extract stool?** Suggests defaecatory disorder.
- **What is the urge frequency?** – Daily suggests normal transit; every 2 days or less suggests slow transit.
- **Any clear precipitants to onset?** Abdominal or pelvic surgery, childbirth or emotional trauma.
- **Faecal impaction and faecal soiling?** Suggests idiopathic megacolon.
- **Alarm symptoms** needing urgent imaging:
  - Rectal bleeding;
  - Recent onset of symptoms;
  - Weight loss;
  - Family history of colon cancer.
- **Comorbid medical history: thyroid disease, diabetes or renal impairment?**
- **Drug history** (see Table 3.3).
- **Dietary history**: specifically meal frequency and fibre intake.

Investigations

- **Blood tests**:
  - FBC: for anaemia if colon cancer is the cause of constipation;
  - U&E: uraemia as a cause of constipation;
  - Thyroid function tests: hypothyroidism as a cause of constipation;
  - Calcium: hypercalcaemia as a cause of constipation;
  - Glucose: diabetes, constipation is the commonest GI manifestation.
- **Imaging**:
  - Colonic imaging to exclude cancer if there are any alarm symptoms, or in patients over 50 years of age who have a new onset of symptoms: colonoscopy **or** barium enema **or** CT colonography (for details, see Chapter 6);
  - Evacuation proctography (by barium or MRI contrast) allows study of anorectal morphology and dynamics during defaecation. It detects:
    - Functional abnormalities such as inco-ordination of the pelvic floor and anal sphincters;
    - Structural abnormalities of rectal emptying such as intussusception, rectal prolapse and rectocoele;
  - Radio-opaque marker study of whole gut transit – a useful measure of the motor function of the whole gut. Whole gut transit can be measured by performing an abdominal X-ray after the ingestion of radio-opaque markers; it primarily reflects colonic transit, given that intestinal transit time is mostly colonic;
  - Plain abdominal X-ray is *not* a sensitive diagnostic test of constipation.

- **Anorectal physiological tests**. These are only needed in the minority of patients who do not respond to lifestyle advice or brief laxative use:
  - Recto-anal inhibitory reflex: presence excludes Hirschsprung's disease;
  - Ano-rectal sensory testing: to detect whether there is loss of rectal sensation (in patients with multiple sclerosis, Parkinson's disease, etc.).

Treatment

- **Diet**: in general, patients with normal transit need to augment dietary fibre and liquid intake. Only if they cannot manage this through normal diet should they be prescribed fibre supplements. Patients with slow transit, by contrast, need less fibre in their diet since fibre tends to exacerbate bloating and does not help accelerate transit.
- **Laxatives**:
  - Stimulant laxatives (senna, bisacodyl) are best used on an as-required basis, rather than regularly, to avoid laxative dependence;
  - Stool softeners (docusate) are primarily used as adjuvant agents;
  - Osmotic agents (magnesium salts, lactulose) are effective in slow transit and allow dose adjustment according to response, but may be unpalatable.
- **Biofeedback**: behavioural therapy with biofeedback is an effective alternative to laxatives for patients who want to avoid long-term dependence on drugs.
- **Surgery**: whilst rectocoele or pelvic floor repairs may help some patients with structural rectal or pelvic abnormalities, colonic resection surgery for constipation has mostly fallen out of favour (due to poor long-term results and the frequent need for re-operation).
- **Psychological therapy**: some patients with constipation have the symptom as a consequence of significant psychological distress, and in these situations specific psychological help can be helpful.

Diarrhoea

Diarrhoea is strictly defined as an increase in stool weight above 200 g – mostly occurring as a result of an increase in stool water content.

PHYSIOLOGY OF FLUID FLUXES IN THE GUT

Fluids into lumen		Fluids out of lumen	
Food in	*2000 ml*	Small bowel reabsorption	5350 ml
Saliva	250 ml	Colonic reabsorption	2000 ml
Gastric secretions	2000 ml	*Stool volume*	*150 ml*
Small intestinal secretions	3250 ml		
TOTAL	7500 ml	TOTAL	7500 ml

The above illustrates the approximate fluid fluxes in the gut in a healthy, well nourished individual. It illustrates the principle that two-thirds of the reabsorption of liquid is accomplished during the rapid period of transit (approximately 2–4 h) through the small bowel. This leaves approximately 2 l of material entering the caecum each day, which gets progressively dehydrated in its passage through the colon over approximately 24 h. It is readily appreciable therefore that small changes in colonic function will alter stool volume: a 10% reduction in colonic reabsorption will leave an extra 200 ml of liquid in the lumen, and more than double the stool volume.

The prevalence of chronic diarrhoea (>4 weeks of symptoms) is approximately 4% in the community population in the UK. Whilst a comprehensive list of causes of diarrhoea is given in Table 3.4 (for examination revision purposes), it is easier to remember this list by considering the potential causes of diarrhoea. Many disorders cause a mixture of the three basic mechanisms.

Mechanisms of diarrhoea

Osmotic diarrhoea

- **Principle**: persistence of non-absorbed osmotically-active compounds (typically carbohydrates or fat) which retain fluid in the lumen exceeding the colonic capacity to reabsorb.

Table 3.4 Causes of diarrhoea.

Condition	Comments	Frequency
Gastroenteritis	Virus	Commonest
	Bacterial (*Campylobacter, Salmonella)*	Common
	Toxin *(E. coli, Shigella)*	Common
	Parasite (*Giardia)*	Rare
Inflammatory bowel disease		Common
Drug-induced	Many, including alcohol, antibiotics, Mg-containing antacids, PPIs, NSAIDs	Common
Colorectal carcinoma	Left sided > right sided	Common
Irritable bowel syndrome (IBS)	Diarrhoea-predominant IBS may complicate prior gastroenteritis in 25% of cases	Common
Coeliac disease	>50% of patients report diarrhoea	Unusual
Microscopic colitis	Diagnosis depends on right colon histology	Unusual
Laxative misuse	High level of suspicion needed to avoid unnecessary investigation	Unusual
Bacterial overgrowth	Usually as comorbidity of another disorder	Unusual
Uncommon gut disorders	Pseudo-membranous colitis	Unusual
	Post-gastric or ileal resection or vagotomy	Unusual
	Ischaemic colitis	Unusual
	Lactose intolerance	Unusual
	Bile acid malabsorption	Rare
	Whipple's disease	Rare
	Gastrinoma/VIPoma	Rare
	Carcinoid	Rare
Non-intestinal disease	Chronic pancreatitis	Unusual
	Thyrotoxicosis (may be no other clinical signs)	Unusual
	Autonomic neuropathy (diabetes)	Rare
	Addison's disease	Rare
	Behçet's disease	Rare
	Hypoparathyroidism	Rare
Infiltrative gut diseases	Amyloidosis	Rare
	Intestinal vasculitis	Rare
	Mastocytosis	Rare
	Hypogammaglobulinaemia	Rare

- **Characteristic**: 'porridgey' stool; symptoms resolve on fasting.
- **Investigation**: rarely needed, but physiologically gratifying. Identifies an increased faecal osmotic gap: $290 - 2 \times ([\text{faecal } Na^+] + [\text{faecal } K^+])$; a gap >125 mOsm/kg is diagnostic.
- **Causes**:
  - Laxative misuse (lactulose or other osmotic laxatives);
  - Lactose intolerance (most commonly as part of another intestinal disorder, such as Crohn's disease, coeliac disease);
  - Bacterial overgrowth (due to production of osmoticaly-active compounds by small bowel bacterial colonisation);
  - Steatorrhoea causes (chronic pancreatitis, small bowel disease).

Secretory diarrhoea

- **Principle**: small bowel secretion abnormally stimulated by a peptide (vasoactive intestinal peptide [VIP] or gastrin) or a toxin (*Escherichia. coli* enterotoxin, *Vibrio cholera* toxin). The causative agents act on cyclic nucleotide release within enterocytes, resulting in ion secretion and water loss into the lumen.
- **Characteristic**: 'watery' stool in huge volumes; does not settle with fasting.

- **Investigation**: rarely needed, but stool volumes usually >500 ml/day, with normal faecal osmotic gap (<50 mOsm/kg).
- **Causes**:
  - Toxins (*E. coli, V. cholera, Clostridium*);
  - Tumour (VIPoma, Zollinger–Ellison, bile acid malabsorption, villous adenoma).

Dysmotility diarrhoea

- **Principle**: accelerated transit leaves less time for reabsorption in small and/or large bowel.
- **Characteristic**: stool consistency varies day to day.
- **Investigation**: none, other than an accurate history.
- **Causes**:
  - IBS;
  - Post GI resection;
  - Drugs (stimulant laxatives).

History

- **Nature of diarrhoea**: watery, 'porridgey' and variable consistency stool – as above; pale, fatty stools that are hard to flush away suggest steatorrhoea (pancreatic or small bowel cause).
- **Timing**: night-time diarrhoea is organic and excludes a diagnosis of IBS; morning diarrhoea suggests inflammatory bowel disease (IBD), IBS or alcohol misuse.
- **Associated features**:
  - Overt blood loss suggests a colonic cause; Weight loss warrants urgent investigation;
  - Drug and surgical history (as per Box 3.1);
  - Systemic illness (diabetes, scleroderma, thyroid disease);
  - Family history (colorectal cancer, IBD, coeliac disease).

Rigid sigmoidoscopy is a useful part of the clinical assessment of the patient with diarrhoea – distal tumours, ulcerative colitis and infectious proctitis are readily evident, and biopsies can be taken (*Note*: microscopic colitis cannot be excluded by rectal biopsies alone).

Investigation

- **Stool microscopy**: for *Giardia* (and other parasites or ova).
- **Other stool tests**:
  - *Clostridium difficile* toxin (if recent antibiotics);
  - Culture (if suspect food poisoning with *Salmonella, Shigella, Campylobacter*);
  - Electron microscopy for viruses is rarely if ever needed;
  - Faecal calprotectin (a neutrophil-derived peptide) is emerging as a potentially useful tool to identify IBD or cancers as opposed to IBS.
- **Blood tests**:
  - Haemoglobin: carcinoma, IBD, coeliac disease;
  - MCV elevated in coeliac disease (low folate), terminal ileal disease (low B_{12}), Crohn's, post-resection, alcohol misuse;
  - MCV reduced in carcinoma, IBD;
  - Serum potassium: classically low in VIPoma, but also in any severe diarrhoea (small bowel K^+ loss);
  - CRP (preferred to ESR) elevated in carcinoma (mild increase), IBD (greater increase) and infection (most elevated);
  - TFTs;
  - Coeliac antibodies (see p. 88).
- **Endoscopy**:
  - Upper GI endoscopy and D2 biopsy: if suspect coeliac disease or *Giardia;*
  - Flexible sigmoidoscopy: if diarrhoea associated with fresh rectal bleeding;
  - Colonoscopy and ileoscopy with biopsies: for all patients if stool and blood tests normal; intention is to exclude cancer and IBD.
- **Radiology**:
  - Barium enema: not a good test for diarrhoea (poor mucosal definition of subtle lesions, no opportunity to obtain histology);
  - CT colonography: if patient unsuitable or unfit for colonoscopy;
  - Abdominal ultrasound or CT scan: if biliary or pancreatic disease suspected;
  - Barium follow-through: to exclude Crohn's disease, or intestinal lymphoma.
- **Further investigation**:
  - If above investigations do not reveal a cause, may need to consider admission for observation (food and stool chart) and 3-day stool weight estimation. If diarrhoea settles, or stool weight <200 g/day, treat as IBS or functional (laxative misuse); if stool weight >200 g/day, then further investigation is warranted;
  - Stool osmolality and volume after a 48-h fast will identify secretory and osmotic causes of diarrhoea;

- Laxative screen in suspected patients: this will need stool and serology samples;
- Capsule enteroscopy: pick up for diarrhoea is poor if barium follow- through is normal;
- Lactose hydrogen breath test will identify hypolactasia, but it may be more practical to ask the patient to empirically follow a lactose-free diet and see how they respond;
- Se-HCAT bile acid malabsorption test may be helpful, but an empirical trial of treatment with cholestyramine may be appropriate.

Treatment

Treatment is usually directed towards supportive care (maintaining fluid balance, treating pyrexia) and correcting the underlying cause. Symptomatic treatment may be undertaken with:

- Loperamide: acts on μ-opioid receptors in the myenteric plexus of the gut to reduce peristalsis and intestinal secretion; it does not cross into the CNS or cause dependence;
- Codeine: an opiate with analgesic and antidiarrhoeal properties; it can cross into the CNS and cause drowsiness and, in large doses, respiratory depression;
- Co-phenotrope: a combination drug of a synthetic opiate and atropine (anticholinergic) which reduces intestinal secretion and contraction; the anticholinergic effects mean it is often poorly tolerated.

Anal incontinence

This refers to involuntary passage of rectal content (gas or stool), and it is a source of major embarrassment to the sufferer. The symptom occurs more commonly with age, and on a weekly basis in 2% of community-dwelling over-70-year olds.

Incontinence arises when there is disturbance of the:

- Anus;
- Rectum; or
- Co-ordination between anus and rectum.

In turn, this could be due to either disorder of structure or function of either organ. With regard to function, anal incontinence can be due to either disturbed motor or sensory function. The overall possible pathophysiology is summarised in Figure 3.1, which also outlines the possible causes and relates these to the pathophysiology.

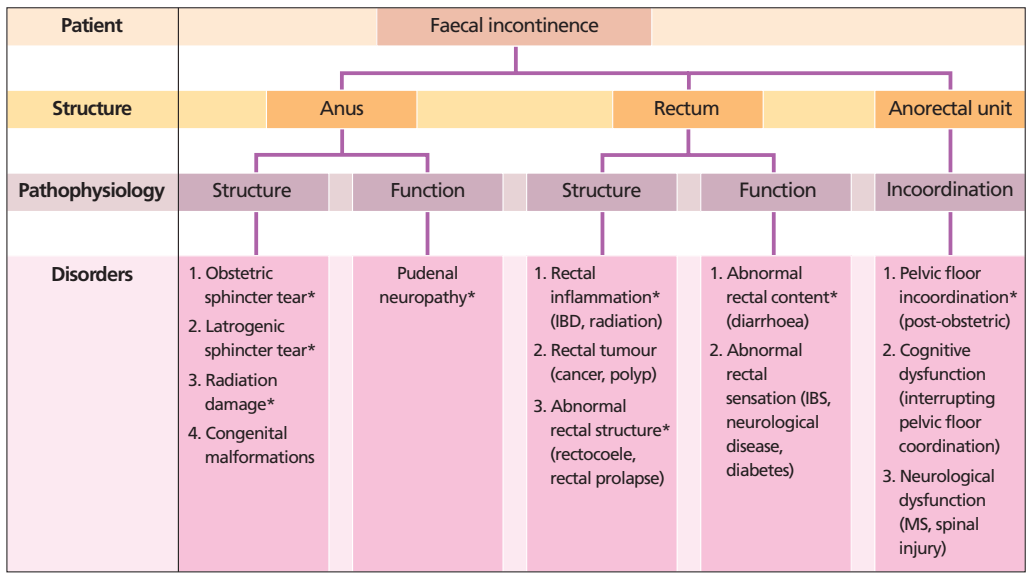

Figure 3.1 Pathophysiology of faecal incontinence. The most common disorders are indicated with an asterisk. IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MS, multiple sclerosis.

History

There are two forms of anal incontinence:

- **Urge incontinence** occurs when there is marked urgency to void the bowel, with incontinence occurring before the patient can get to a toilet;
- **Passive incontinence** is due to leaking of stool without perception of any urge.

History taking should also address the severity of the condition (need to wear pads, frequency of episodes, effects on lifestyle).

Investigations

- **Structure**: anal inspection, endo-anal ultrasound (rarely pelvic CT or MR);
- **Function**: digital examination, anorectal manometry and sensory testing (rarely EMG).

Treatment

- **General**:Optimise stool consistency (antidiarrhoeal drugs – loperamide, codeine);
  - Dietary advice (rationalise dietary fibre intake, avoid excess caffeine, alcohol);
  - Review medications (if possible, discontinue any that cause diarrhoea);
  - Anal sphincter exercises.
- **Specific**:
- Sphincter tear: surgical repair (when possible);
- Rectal prolapse or rectocoele: surgical repair;
- Disease causes diarrhoea: specific medical treatment of each condition;
- Pelvic inco-ordination: biofeedback or sacral nerve stimulation (surgical procedure to electrically stimulate sacral nerves and hence improve sphincter function).

Weight loss

Weight loss is a common cause for presentation to gastroenterology services. It should be remembered that there are 'physiological' reasons for weight loss, according to the simplistic formula:

Body weight = Food ingested
–Exertion undertaken

In other words, reduced nutrient intake or excess exercise cause weight loss. Importantly, there are many non-GI causes of weight loss (Table 3.5).

Table 3.5 Causes of weight loss.

Gastrointestinal	Oral disease GI malignancy Small bowel malabsorption Pancreatic disease Liver cirrhosis Inflammatory bowel disease (Crohn's > ulcerative colitis) Gut infestations (*Giardia,* small intestine bacterial overgrowth) Chronic intra-abdominal sepsis
Psychosocial	Eating disorders (anorexia > bulimia) Affective disorders Alcohol misuse (multifactorial) Chronic pain syndromes Starvation
Metabolic	Diabetes (type I especially) Hyperthyroidism Addison's disease Hypopituitarism Uraemia Chronic heart failure ('cardiac cachexia')
Chronic inflammatory diseases	Rheumatoid arthritis Connective tissue disorders Chronic obstructive pulmonary disease
Chronic infectious disease	Tuberculosis HIV/AIDS Abscesses
Malignancy anywhere	Especially common sites (lung, breast, cervix, prostate, lymphoma)

Causes

See Table 3.5.

History and investigation

Table 3.5 lists the conditions that should be considered in assessing weight loss. Particular attention should focus on the psychological and environmental factors that may be influencing nutrient intake, and hence weight.

Body mass index (BMI) is used as the measure of weight that takes into account height. BMI is calculated as weight (in kg) divided by (height)^2 (in m^2). A value between 20 and 25 is normal, but sequential measurements showing a progressive reduction, even if within this normal range, should not be ignored.

Iron-deficiency anaemia

Iron-deficiency anaemia occurs in up to 5% of men and post-menopausal women in the UK. It is a common cause of referral to a GI clinic for assessment, since the cause is often due to GI blood loss or nutrient malabsorption. In one-third of patients, the cause is never identified. The important diagnoses to exclude are colorectal cancer, IBD and hereditary telangiectasia or colonic arteriovenous malformations. Therefore, the following findings do not preclude the need to image the whole colon:

- Oesophagits;
- Hiatus hernia;
- Non-bleeding peptic ulcer;
- Haemorrhoids;
- NSAID usage.

The causes can be broadly thought of as being due to either insufficient iron intake or excessive losses (from the gut or gynaecological system).

PHYSIOLOGY OF IRON METABOLISM

Normal daily dietary intake of iron is approximately 15 mg. Gastric acid is essential to release iron from food and maintain it in the soluble ferrous (Fe^{2+}) form; this is why achlorhydria may cause iron deficiency. Ferrous iron is then absorbed through an active process in the duodenum and jejunum. Maximal absorption is between 2 and 4 mg/day, being at the upper figure when iron stores are low or there is chronic hypoxia. Absorbed iron can then be stored in the enterocytes as ferritin or can be bound to the protein transferrin and circulated around the body.

Assessment

- **Condition**: angular stomatitis, glossitis, cheilosis, koilonychias.
- **Cause**:
  - Dietary history;
  - Drug history;
  - History of overt blood loss;
  - Any associated features (diarrhoea, mouth ulcers, weight loss);
  - Family history;
  - Abdominal mass.
- **Complications**: features of anaemia (malaise, exertional dyspnoea, heart failure).

Investigation

- **Condition**:
  - Blood tests:
    - Hb (<13.5 g/dl men; <11.5 g/dl women)
    - MCV < 80 fl
    - MCH < 27 pg
  - Blood film: severe iron-deficiency shows dimorphic pattern or Howell–Jolly bodies;
  - Consider Hb electrophoresis if a haemoglobinopathy is a possibility;
  - Iron studies:
    - Plasma iron is a measure of available iron (↓ in iron deficiency and anaemia of chronic disease)
    - Ferritin – most sensitive measure: ↓ in iron deficiency (normal or ↑ in chronic disease)
    - Transferrin saturation: less specific than ferritin (↓ in iron deficiency and anaemia of chronic disease)
    - Total iron-binding capacity: an indirect measure of serum transferrin and so is the inverse of the transferrin situation (↑ in iron deficiency).
- **Cause**:
  - Endomysial antibodies: not preferred to distal duodenal histology;
  - Upper GI endoscopy and distal duodenal antibodies;
  - Colonoscopy is preferred to barium enema or CT colonography (allows option of taking biopsies and treating any bleeding vascular lesions);
  - Further investigations: if appropriate investigations above are normal, then one can consider:
    - Meckel's diverticulum in young patients
    - Capsule enterosocopy is helpful in some refractory patients
    - Abdominal ultrasound (renal cell carcinoma)
    - Mesenteric angiography (coeliac and superior mesenteric vessels) is only indicated if there is overt bleeding

– Laparotomy and on-table colonoscopy is hardly ever needed, being reserved for cases of catastrophic bleeding complicating iron deficiency.

Management

If asymptomatic, give oral iron until Hb is normalised; an increase of 0.5–1 g/dl perweek can be expected. Treatment is continued for a further 3 months to replace iron stores, then stopped, and the FBC repeated 3 months later. If further iron-deficiency anaemia has recurred, a review of investigations is needed. If this too is normal, watchful waiting with courses of oral iron as required is appropriate.

Parenteral iron is only needed if the patient is intolerant of, or malabsorbing, oral iron. The risks of anaphylaxis with intravenous iron mean that a test dose needs to be given.

4

Nutrition

Nutritional assessment is directed towards:

- Calorie–protein status;
- Specific mineral and vitamin status.

Nutritional physiology

Glucose is essential to metabolism in the brain and renal medulla, and to red cell metabolism. Other organs mainly use fatty acids to produce energy. For this reason, under normal circumstances, regulatory mechanisms maintain and control glucose levels in a tight range both around the time of eating and between meals. Insulin is the main glucose regulatory hormone. On eating, glucose is rapidly absorbed into the portal system, resulting in insulin secretion from the pancreas and a rise in insulin levels. Under the influence of insulin, the liver extracts a large percentage of that glucose and converts it to glycogen. Again under the influence of insulin, glucose reaching the periphery is taken up first into muscle and then into adipocytes.

Between meals glucose levels in the portal tract fall and the resultantdecrease in insulin secretion prompts glycogenolysis, gluconeogenesis and lipolysis. Glycogenolysis occurs in the liver in order to maintain plasma glucose levels. At the same time, lipolysis is induced and fatty acids are released and become the major energy substrate for the body. Gluconeogenesis is induced in concert with glycogenolysis, converting glycerol, amino acids and fatty acids (via the citric acid cycle) to glucose.

Other hormones act on the regulatory mechanism but their effect is limited compared to insulin, except in times of stress. They include glucagons, catecholamines and growth hormone. They have an anti-insulin effect, increasing glycogenolysis, gluconeogenesis and release of fatty acids and glycerol from adipose tissue, and amino acids from muscle.

Lipids enter the circulation as chylomicrons. These are large droplets of triglyceride emulsified by a surface monolayer of phospholipid and apolipoproteins. The apolipoproteins are transferred onto the chylomicrons from high-density lipoproteins (HDLs). When chylomicrons reach the peripheral capillaries of the heart and adipose tissue, lipoprotein lipase on the capillary endothelium binds them, and the triglycerides at the core of the chylomicron are rapidly hydrolysed to fatty acids that are then taken up and utilised by peripheral tissues. HDL recycles the remaining surface phospholipids and apolipoproteins. Between meals chylomicrons disappear from the circulation and are replaced by very low-density lipoproteins (VLDLs), which are secreted by the liver. They are bound and metabolised by lipoprotein lipase in peripheral capillaries also.

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Anton Emmanuel and Stephen Inns.

Evaluation of nutritional status

About 30% of all patients in hospital are undernourished. A large number of these patients are undernourished when admitted to hospital and in the majority of these undernutrition develops further while in hospital. Given that nutritional status contributes directly to morbidity and mortality in the majority of medical conditions, accurate and timely assessment of nutritional status and identification of patients needing nutritional input is essential. This assessment takes two forms:

- Nutritional screening, either in the community or at hospital admission;
- Nutritional assessment, a more detailed assessment, performed by a nutrition expert and reserved for those patients identified by screening as being at nutritional risk.

Nutritional screening

Nutritional screening should be rapid and simple. It is conducted by admitting staff in the hospital, or the community healthcare team. All patients should be screened on admission to hospital. The aim is to stratify patients into nutritional risk groups and thus decide which patients should be referred on for further nutritional assessment and support, which can be managed using a nutrition plan as a part of the ordinary ward or home routine, and which are not at risk of malnutrition, but may need to be rescreened at specified intervals.

Nutritional assessment

The nutritional assessment is more detailed than screening and includes a full history, clinical examination (Table 4.1) and, where appropriate, laboratory investigations. An expert clinician, dietician or nutrition nurse conducts it. It in turn leads to a nutritional support plan. Following initial assessment, nutritional and fluid status assessment is a continual process conducted by nursing, medical and dietetic staff, gauging the patient's ability to manage oral supplements, enteral feeding and/or parenteral feeding, with appropriate adjustments if requirements are not met.

Nutritional support

Nutritional support simply refers to the provision of nutrition above and beyond the normal diet and includes food fortification, oral nutritional supplementation (ONS), tube feeding and parenteral nutrition (PN) (Figure 4.1 and Box 4.1). It aims for increased intake of macro- and/or micro-nutrients. In certain circumstances a patient may receive one or a combination of modalities of support.

In general, the following principles are adhered to:

- High catabolic states need high calorie and nitrogen intake;
- Enteral feeding is preferred to parenteral feeding, and oral feeding is preferred to enteral feeding;
- A multidisciplinary team should determine nutritional needs and route of supplementation.

Five factors need consideration in deciding the replacement schedule:

- Calorie (fat and carbohydrate) requirement;
- Nitrogen (protein) balance;
- Minerals and vitamins;
- Fluid and electrolytes;
- Fibre.

Calorie replacement

Consideration of nutritional support is required when there has been >10% change in body weight, and depends on the specific illnesses surrounding the weight loss:

- General = highly catabolic states = 50 kcal/kg/24 h:
  - Intensive care, burns;
  - Chronic sepsis;
  - Following major surgery;
  - Malignancy.
- Gastrointestinal = intermediate catabolic states = 40 kcal/kg/24 h:
  - Intestinal fistula;
  - Short bowel syndrome;
  - Acute pancreatitis;
  - Crohn's disease;
- Prolonged inadequate dietary intake = low catabolic states = 30 kcal/kg/24 h:
  - Dysphagia post-cerebrovascular accident (CVA);
  - Neurological illness.

Table 4.1 Clinical manifestations of specific deficiency states.

Clinical	Deficiency	Measurement
Anorexia	Calories and protein	Subjective
Weight	Calories and protein	BMI <20 kg/m^2 Triceps skinfold thickness Mid-arm muscle circumference
Muscle wasting, oedema	Protein	Albumin <35 g/l Transferrin <2 g/l
Glossitis, cheilitis, stomatitis, koilonychias	Iron	Serum iron ↓ Serum ferritin ↓ Iron-binding capacity ↑
Weakness, proximal myopathy, tetany, paraesthesiae Chvostek and Trousseau signs	Calcium	Serum calcium ↓
Weakness, proximal myopathy, tetany, paraesthesiae	Magnesium	Serum magnesium ↓
Proximal myopathy	Phosphate	Serum phosphate ↓
Anorexia, diarrhoea, depression, anaemia, rash	Zinc	Serum zinc ↓
Night blindness, xerophthalmia	Vitamin A	Dark adaptation time
Bone pain, proximal myopathy.	Vitamin D	Serum calcium ↓ Serum phosphate ↓ Alkaline phosphatase ↑ Bone X-ray, bone biopsy
Easy bruising	Vitamin K	INR >1.3
Peripheral neuropathy, psychosis, ophthalmoplegia	Vitamin B_1	Red cell transketolase
Stomatitis, anaemia, ataxia, mucosal fissures	Vitamin B_2	Red cell glutathione reductase
Diarrhoea, dermatitis, dementia	Nicotinamide	Urinary metabolites
Peripheral neuropathy, sideroblastic anaemia	Vitamin B_6	Aminotransferase activity
Peripheral neuropathy, macrocytic anaemia, subacute cord degeneration, vegans	Vitamin B_{12}	Serum B_{12}↓
Macrocytic anaemia, alcoholics	Folate	Serum folate ↓
Bleeding, periosteal haemorrhages, poor wound healing, gum hypertrophy	Vitamin C	White cell ascorbic acid

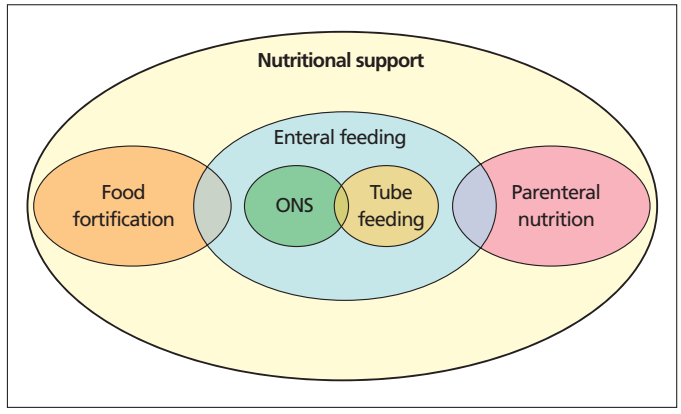

Figure 4.1 Range of options for nutritional support.

Box 4.1 Methods of delivery of nutritional replacement.

Oral

- A variety of nutritional supplements are available
- Amount required is judged according to actual oral intake

Nasogastric feeding

- Appropriate for patients needing up to 4 weeks of feeding
- If there is gastric emptying delay, nasojejunal tubes may be used

Gastrostomy feeding

- Percutaneous endoscopic gastrostomy (PEG) tubes used if >4 weeks of feeding needed
- Jejunostomy extensions can be placed if there is gastric emptying delay or risk of aspiration with gastric feeding
- Home PEG feeding with small domestic feeding pumps is feasible

Parenteral feeding

- Careful balance of nitrogen and electrolytes is required
- Tunnelled central venous lines are preferred to peripheral lines (due to risk of sepsis and clotting)
- Home parenteral nutrition is needed for some patients with intestinal failure

Protein replacement

In a healthy individual the protein requirement is 0.12 g nitrogen/kg body weight/day (1 g nitrogen per 6.25 g protein on average). Patients with protein malnutrition, inflammatory or infective disease and other catabolic conditions (e.g. surgery, burns) will have greater requirements. In the severely unwell, aiming for a positive nitrogen balance is often not possible or advisable, as nitrogen losses actually increase with increasing nitrogen intake, and high nitrogen intakes lead to metabolic burden. Generally, in unwell patients, provision of 0.20 (0.17–0.25) g nitrogen/kg body weight/day should be sufficient.

Mineral, vitamin and trace element replacement

Protein energy malnutrition particularly predisposes to deficiencies of micronutrients and these should be corrected. For ONS and tube feeds the vitamin and trace element content is regulated. As these recommendations are based on a daily intake of 2000 kcal, advice from a dietician should be sought about the most appropriate enteral feeds and micronutrient supplements to use for an individual patient.

Fluid and electrolyte replacement

Usually between 1.5 and 3.0 l of fluid are given to adults receiving enteral or parenteral nutrition (PN). In general 30–35 ml/kg body weight/day of fluid is required, with additional requirements for those with fever and losses of other body fluids. Electrolyte requirements vary greatly and should be tailored to the individual by monitoring serum, and in some circumstances urinary electrolytes. In general 1–1.5 mmol/kg/day of sodium, chloride and potassium and 0.3–0.7 mmol/kg/day of phosphate is appropriate. In standard enteral and parenteral regimens, daily intakes of sodium are 80–100 mmol, potassium 60–150 mmol and phosphate 15–40 mmol. Daily weighing, fluid intake charts, serum biochemistry and daily examination of the patient (for dehydration, oedema), etc. are necessary for monitoring.

Fibre replacement

Soluble fibres have a prebiotic effect (i.e. stimulate growth of beneficial bifidobacteria and lactobacilli) and on fermentation provide short-chain fatty acids which are essential to the metabolism of the cells lining the colon. Less soluble fibre acts as a bulking agent, increasing stool output and frequency, and reducing colonic transit time. Patients receiving enteral nutrition may benefit from feeds containing a mix of insoluble and soluble fibres, particularly if long-term tube feeding is their sole source of nutrition, in order to maintain gut integrity, function and flora. For those receiving PN, it is acknowledged that to maintain gut integrity and function, where possible and appropriate, some feeding into the gut should be maintained.

Parenteral nutrition

Indications

It is clear that in patients with complete, irreversible intestinal failure, PN support is life saving.

However, the use of PN in other clinical situations, often for short-term use, is more controversial. Although meta-analyses have not shown improvements in clinical outcome with PN overall, they have shown improvements in complication rates among malnourished patients. In general, PN should only be considered when partial or complete intestinal failure has occurred and oral nutrition or enteral tube feeding (ETF) is not possible or has failed.

Administration

The GI tract should be utilised as much as possible in order to maintain gut hormonesecretion, enzyme production, mucosal absorptive capacity and resistance to bacterial translocation. When a patient is on PN, they should be reassessed regularly with the aim of transferring to oral feeding or ETF.

Access is via a dedicated feeding line. This can be either a peripheral feeding line or central venous catheter. Peripheral lines give ease of venous access but peripheral veins cannot tolerate high infusion rates or high osmolarity solutions, such as lipid-free solutions.

Complications

Complications can be divided into line-related complications and metabolic complications.

Line-related complications

Early line-related complications include local haematoma, arterial puncture and pneumothorax. Catheter-related sepsis remains the most serious complication of PN. Meticulous line care is vital and patients with suspected line sepsis should have their PN stopped temporarily and blood cultures taken peripherally and from all catheter lumens. Generally, lines should be removed and replaced after 24 h of appropriate antibiotics. However, it is reasonable to attempt sterilisation of a long-term tunnelled line. Central vein thrombosis is relatively common; however, it is usually not clinically evident.

Metabolic complications

The risk of refeeding syndrome is high and all patients who are to receive PN must be carefully assessed and managed with this in mind. Hyperglycaemia is common and largely due to the insulin resistance associated with severe disease. In the setting of critical illness, benefits have been seen with aggressive management of even minimal hyperglycaemia with the use of intensive insulin therapy.

Abnormal LFTs are common but usually relate to the underlying disease, sepsis and drugs rather than to the PN itself. Steatosis may results from over-administration of glucose and lipid, and is due to the resultant hyperinsulinaemia, lipogenesis and hepatocyte fat deposition. In those receiving long-term PN there is a risk of cholestasis. The exact aetiology of this is unknown but may relate to increased lithogenicity of bile with interruption of enterohepatic bile acid circulation, reduced gallbladder motility and biliary sludge because of no oral intake, bacterial overgrowth and nutrient deficiencies, including choline, taurine and carnitine. Long-term PN also places the patient at risk of metabolic bone disease and micronutrient deficiencies, particularly in the setting of ongoing intestinal loss.

Enteral nutrition

Oral nutritional supplements

The oral route of nutrition should always be preferred. ONS provides macronutrients and micronutrients, usually in a liquid form. Polymeric feeds containing protein, carbohydrate and fat, together with electrolytes, minerals, trace elements and vitamins. These are much more palatable than elemental feeds which contain protein as amino acids and generally have low fat contents, often providing the fat as medium-chain triglycerides.

The main indication for ONSs is the presence of disease-related malnutrition, which may occur in many patient groups, including those with cancer, the elderly, surgical patients and others with severe acute or chronic diseases. Other indications include preoperative preparation of a malnourished patient, inflammatory bowel disease, short bowel syndrome, intractable malabsorption (which can include patients with a range of GI, including pancreatic, and liver diseases), post total gastrectomy, dysphagia, bowel fistulae and dialysis (continuous ambulatory peritoneal dialysis, haemodialysis). Provision of ONS tends not to suppress food intake substantially and so total nutritional intake can be significantly improved.

Enteral tube feeding

ETF should be considered if supplements are insufficient to ensure an adequate intake and recovery, or where oral intake is unsafe and contraindicated. The conditions in which tube feeding should be a part of routine care include:

- Protein-energy malnutrition (>10% weight loss) with little or no oral intake for 5 days;
- <50% of the required oral nutrient intake for the previous 7–10 days;
- Severe dysphagia or swallowing-related difficulties, e.g. head injury, strokes, motor neurone disease;
- Major, full-thickness burns;
- Massive small bowel resection;
- Low-output enterocutaneous fistulae.

ETF is provided by two main routes in the majority of patients: via nasogastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG). Generally administration is via a pump and sterile administration set, delivering continuous infusions of feed over many hours. Sometimes boluses of feed are given with gastric but not jejunal tube feeding.

As inpatients, on the whole, tend to be fed for short periods of time, nasogastric feeding, using a fine-bore feeding tube (polyurethane) is appropriate, at least initially, in most patients. Tubes should be placed by a trained health professional and correct positioning should be checked, by X-ray initially, to ensure there is no malpositioning into the lungs or elsewhere. Some authorities recommend checking tube position by aspirating stomach contents prior to every feeding episode (checking for pH 5 or less using pH indicator paper). Secure fixing of the tube to the nose and face is essential. Where ETF will be longer term, PEG is the most common route used. For patients at increased risk of regurgitation of feed and/or pulmonary aspiration, gastric atony or gastroparesis, post-pyloric feeding into the duodenum or jejunum should be considered.

PEG tube insertion is an invasive procedure requiring careful patient selection and informed consent from the patient and family. Patients should have a recent platelet count, haemoglobin and coagulation screen available. Where possible, antiplatelet drugs and anticoagulants should be stopped prior to the procedure. Antibiotics are administered prior to the procedure to reduce the risk of tube-related infection.

Physiology of starvation

During starvation the body utilises liver glycogen stores as well as gluconeogenesis to form glucose. Gluconeogenesis is glucose synthesis using the breakdown products of lipid and protein. During this process adipose tissue releases large quantities of fatty acids and glycerol, and muscle releases amino acids. With the depletion of glycogen stores, ketone bodies (produced as a by-product of gluconeogenesis) and free fatty acids replace glucose as a major energy source. The result is catabolism of adipose tissue and muscle, with resultant loss of lean body mass.

With refeeding there is a shift from fat back to carbohydrate metabolism. The resultant glucose load triggers insulin release, which in turn increases cellular uptake of glucose, phosphate, potassium, magnesium and water, and promotes protein synthesis. It is these nutrient, electrolyte and fluid fluxes that can produce the refeeding syndrome (see below).

The refeeding sydrome

The refeeding syndrome can be defined as a syndrome consisting of metabolic disturbances that occur as a result of reinstitution of nutrition to patients who are starved or severely malnourished. At-risk patients include those with:

- Kwashiorkor or marasmus, anorexia nervosa, or other causes of chronic malnutrition (e.g. from carcinoma or in the elderly);
- Chronic alcoholism;
- Prolonged fasting (e.g. hunger strikers);
- Following duodenal switch operation for obesity;
- Oncology patients receiving prolonged chemotherapy;
- Postoperative patients.

Body–fluid fluxes can result in cardiac failure, dehydration or fluid overload, hypotension, prerenal failure and sudden death. The major metabolic disturbances, their pathological basis and treatment are summarised in Table 4.2.

Refeeding syndrome must be considered in any patient who is to receive nutrition, be it oral, enteral or parenteral, after a period of starvation or reduced nutritional intake. Electrolyte disor-

Table 4.2 Nutrient deficiencies in refeeding syndrome: their consequences and management.

Nutrient/electrolyte disturbance	Normal physiology	Consequences of disturbance	Treatment
Hypophosphataemia	Body phosphate 500–800 g 80% in bony skeleton and 20% soft tissues and muscle Major intracellular anion Transcellular movement results from carbohydrate or lipid ingestion and acid–base alterations Intake about 1 g/day: • 80% absorbed in the jejunum • Found in protein-rich food cereals and nuts Output: • 90% renal • 10% GI loss Important intracellular buffer Structural role as a component of phospholipids, nucleoproteins and nucleic acids Central role in cellular metabolic pathways including glycolysis and oxidative phosphorylation. Essential in 2,3-diphosphoglycerate	Skeletal muscle weakness and myopathy Cardiomyopathy Seizures, perturbed mental state and paresthesia Prolonged hypophosphataemia osteomalacia Rhabdomyolysis Thrombocytopenia, impaired clotting processes Reduced leucocyte phagocytosis and chemotaxis Haemolysis Erythrocyte 2,3-diphosphoglycerate depletion, resulting in a leftward shift in haemoglobin–oxygen dissociation curve (i.e. haemoglobin has a greater affinity for oxygen)	Severe hypophosphataemia rare, most cases are clinically insignificant Treatment only if plasma phosphate concentration <0.30 mmol/l or symptomatic Intravenous phosphate replacement with the Vannatta regimen: • 9 mmol of monobasic potassium phosphate in half-normal saline continuous intravenous infusion over 12 h • Not with hypercalcaemia (risk of metastatic calcification) or hyperkalaemia • Plasma phosphate, calcium, magnesium and potassium monitored closely • Infusion stopped once plasma phosphate >0.30 mmol/l

(*continued*)

Table 4.2 Nutrient deficiencies in refeeding syndrome: their consequences and management (*continued*)

Nutrient/electrolyte disturbance	Normal physiology	Consequences of disturbance	Treatment
Hypomagnesaemia	Mandatory for optimal cell function Cofactor to many enzymes Found mainly in bone and muscle Largely absorbed in the upper small intestine 70% of dietary magnesium eliminated in faeces Major excretory route is through the kidneys	Hypomagnesaemia, defined as <0.5 mmol/l or if symptomatic Mechanism likely multifactorial: • Intracellular flux with carbohydrate feeding • Poor dietary intake • Pre-existing poor magnesium Severe hypomagnesaemia: • Cardiac arrhythmias • Torsade de pointes • Abdominal discomfort • Anorexia • Tremor • Paresthesia • Tetany • Seizures • Irritability • Confusion • Weakness • Ataxia	Can be corrected by oral magnesium but salts poorly absorbed and lead to GI upset Intravenous replacement: • Magnesium sulphate (50% solution containing 2.1 mmol/ml) • 24 mmol of magnesium sulphate over 6 h • Close monitoring of plasma magnesium May facilitate treatment of refractory hypokalaemia Plasma calcium concentration also should be checked
Thiamine deficiency (vitamin B^1)	Carbohydrate refeeding causes increased cellular thiamine utilisation	Wernicke's encephalopathy: ocular disturbance, confusion, ataxia and coma, Korsakov's syndrome: short-term memory loss and confabulation	50–250 mg thiamine should be given at least 30 min before refeeding is instigated More thiamine might be necessary until the patient is stabilised NB: some preparations associated with anaphylaxis Oral thiamine can be given as 100-mg tablets once daily
Hypokalaemia	Regulated by the kidney distal nephron Increased by aldosterone, alkalosis Essential for maintaining cell-membrane action potential	Clinical manifestations rare unless severe (<3.0 mmol/l): • Cardiac: arrhythmias, hypotension and cardiac arrest • Gastrointestinal: ileus and constipation • Neuromuscular dysfunction: weakness, paralysis, paresthesia, confusion, rhabdomyolysis and respiratory depression • Potentiation of digitalis toxicity • Glucose intolerance • Metabolic alkalosis • Worsening of hepatic encephalopathy	Cautious intravenous potassium administration Ideally, the rate should not exceed 20 mmol/h and should not be >40 mmol/l in the intravenous infusion mixture Close monitoring of plasma potassium is important Electrocardiographic monitoring preferable

ders must be corrected and the patient made fluid replete prior to beginning refeeding. At-risk patients must be monitored closely, in particular their vital functions, fluid balance and plasma electrolytes, including magnesium and phosphate. Hypophosphataemia is common not only in refeeding syndrome, being present in 2% of hospital admissions.

Intestinal failure

Intestinal failure (IF) results from loss of absorption due to obstruction, dysmotility, surgical resection, congenital defect or disease, and is characterised by the inability to maintain protein energy, fluid, electrolyte or micronutrient balance. IF can be divided into three types:

- **Type 1**: self-limiting intestinal failure as occurs following abdominal surgery;
- **Type 2**: intestinal failure in severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications;
- **Type 3**: chronic IF requiring long-term nutritional support.

Short bowel syndrome (SBS) is IF resulting from the loss of small intestinal absorptive capacity for anatomical reasons. The normal length of the small intestine ranges from 260 to 800 cm and a patient with <200 cm of viable bowel is at risk of SBS, although methods for measuring residual bowel are inaccurate, making assessment of this risk difficult. Dependence on PN may result when the small intestine is shorter than 100 cm in the absence of an intact and functional colon, or 60 cm in the presence of a completely functional colon. Following shortening, the intestine adapts by increasing villous diameter and height, which in addition to some slight lengthening of the small bowel, increases the absorptive surface. As this process evolves over years, especially in children, some patients may go from being PN dependent to PN independent with time.

The vast majority of cases of IF are related to acquired SBS and result from surgical resection of bowel, related to recurrent Crohn's disease, vascular events such as a mesenteric arterial embolism or venous thrombosis, volvulus, trauma, tumour resection or congenital abnormalities in children. Functional IF results when malabsorption occurs despite intact bowel length. Causes include chronic intestinal pseudo-obstruction syndrome, refractory sprue, radiation enteritis and congenital villous atrophy.

Management of Type 2 intestinal failure

Management of the severely ill patient following major resections of the bowel, and often resultant complications, is of utmost importance to prevent further surgical intervention, and reduce the associated high morbidity, mortality and risk of progression to Type 3 IF. Management of these patients requires a skilled multidisciplinary team combining dieticians, pharmacists, biochemists, enterostomal therapists, nurses, microbiologists, radiologists, pain specialists, surgeons and physicians. Experts in this area recommend a temporal sequence in managing the various facets of intestinal failure in these patients and have coined the term 'Sepsis–Nutrition–Anatomy–Plan' or 'SNAP' approach. In this approach attention is first paid to managing sepsis, in particular draining intra-abdominal collections; then the patient's nutritional status is carefully assessed and rectified; following this the intra-abdominal anatomy is clearly delineated in order to guide further management; finally, a long-term plan for the restoration of intestinal continuity is instituted, often involving medical management of 6 months to a year prior to any further attempt at surgical intervention.

Medical therapy

Medical therapy of IF consists of providing adequate nutrition of macro- and micro-nutrients, sufficient fluid, and correcting and preventing acid–base disturbances. In some patients this may require supplementary enteral nutrition and management of electrolyte and fluid losses: orally using salt solutions, or by subcutaneous or intravenous administration. A proportion of patients will be PN dependent and for them home PN (HPN) is often possible, following a period of hospital management and training.

HPN is associated with a significant risk of complications, including liver and biliary complications, catheter-related infections, catheter occlusion and metabolic bone disease, including osteomalacia and osteopenia. Long-term users accrue a 10–15% yearly chance of dying from a therapy complication. While HPN is clearly

life-saving when required, it is associated with a reduced quality of life compared to patients with SBS not requiring HPN, similar to that experienced by patients with chronic renal failure treated by dialysis.

Surgery and intestinal transplantation

Non-transplant surgical treatment for IF includes approaches that increase nutrient and fluid absorption by either slowing intestinal transit or increasing intestinal surface area. Particularly important is restoration of intestinal continuity, such as reanastomosis of the small intestine with the colon, since it can be performed with a relatively low morbidity and mortality, and often with a good probability of discontinuation of PN therapy because of improved fluid absorption.

Intestinal transplantation is rarely performed (fewer than 20 have been performed in the UK), the number limited by its risk. Three-year patient survival after isolated intestinal transplantation is approximately 70%, which is not comparable with the 90% 3-year survival in at-home, stable, PN-treated patients. Hence imminent liver failure is currently the most appropriate indication, followed by patients failing PN therapy (<20% 1-year survival).

Post-transplant complications include:

- Postoperative haemorrhage;
- Vascular leaks;
- Obstruction;
- Biliary leaks or obstruction;
- Allograft rejection (frequent and may result in graft loss, being most common in the early postoperative period);
- Infection is the leading cause of morbidity and mortality and is a result of the relatively high levels of immunosuppression required and the technically difficult nature of the surgery and aftercare;
- Epstein-Barr virus (EBV) and post-transplant lymphoproliferative (PTLD) disorder are a concern and are more common than in solid-organ transplants;
- Graft-*versus*-host disease (GVHD) is on the whole mild and self-limiting.

5

Gastrointestinal infections

Oral infections

Candidiasis

Candida albicans is a mouth commensal which may proliferate in immunocompromised patients (newborns, AIDS, diabetes, patients receiving cytotoxics) or those taking antibiotics. The diagnosis is usually obvious from the appearance of small white clumps adherent to the mucosa. Dysphagia or painful swallowing raises the possibility of oesophageal involvement. Oral candidiasis is treated with nystatin or amphotericin (which can also be used prophylactically in at-risk patients). Resistant candidiasis, and oesophageal involvement, may require fluconazole.

Vincent's angina

Borrelia vincenti may invade the mucosa in immunocompromised patients or those with appalling oral hygiene. Deep, sloughing ulcers cause severe pain and halitosis; systemic features (fever and malaise) are frequent. Local anaesthetic mouthwashes or oral antibiotics may be needed, depending on severity.

Parotitis

Viral (mumps) or bacterial infections (postoperative) of the parotid glands cause parotid swelling and pain. Oral antibiotics may help, but surgical drainage is required if there is abscess formation. The differential for parotid swelling includes:

- Salivary gland stones;
- Sjögren's syndrome;
- Sarcoidosis;
- Tumours (mostly benign adenoma, rarely mucoepidermoid tumours or cancers).

Oesophageal infections

Oesophageal candidiasis is a common observation at upper GI endoscopy. Less frequent are viral infections, of which herpes simplex is the most important. The features of these are shown in Table 5.1.

Helicobacter pylori infection

Infection with *Helicobacter* is extremely common throughout the world, especially in the developing world. Whilst usually asymptomatic, it is associated with certain disorders (Table 5.2).

H. pylori infection interacts with host factors (age, genetic susceptibility) and environmental factors (smoking, drugs) to result in either:

- Antral gastritis (predisposes to duodenal ulcer); or
- Pan-gastritis (predisposes to gastric carcinoma).

Gastric ulcers are associated with both antral and pan-gastritis.

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Table 5.1 Features of oesophageal infections.

	Candida	Herpes simplex
At-risk groups	Immunocompromised, elderly, antibiotic use	Immunocompromised
Spread	Downwards from mouth	Contagious (other herpes lesions)
Symptoms	Odynophagia, dysphagia	Odynophagia, dysphagia, joint pain
Endoscopic appearance	Creamy plaques, mucosa normal	Mucosal ulceration ± vesicles
Treatment	Fluconazole or amphotericin	Aciclovir
Prognosis	Recurrent, even if correct immune system	Can be eradicated, especially if correct immunocompromise

Table 5.2 Disorders associated with *Helicobacter pylori* infection.

Strong association	Uncertain association
Gastritis (chronic and acute)	NSAID-related ulcer
Peptic ulcer (gastric and duodenal)	Gastro-oesophageal reflux disease
Menetrierer's disease	Functional dyspepsia
Cancer of the stomach	
MALT lymphoma	

Diagnosis

This can be through invasive (endoscopic, shaded in Table 5.3) or non-invasive (breath or blood test, unshaded in Table 5.3) means.

The principle underlying the urea breath test and CLO test are that *H. pylori* produces the enzyme urease which can cleave urea to ammonia and CO_2. In the breath test, ^{13}C or ^{14}C is included in a test meal and can be detected by mass spectrometer (^{13}C) or radiation count (^{14}C). In the CLO test, the biopsies are incubated with urea substrate and a colour pH indicator: ammonia production turns the indicator pink.

Treatment

First-line treatment is 1 week of 'triple therapy', namely a proton pump inhibitor (PPI) and two antibiotics (of amoxycillin, clarithromycin and metronidazole). Second-line treatment involves quadruple therapy, including bismuth-containing preparations or triple therapy incorporating tetracycline. However, in most circumstances, treatment failure is due to poor compliance.

Acute gastroenteritis

Infection in the GI tract usually results in diarrhoea, abdominal pain and occasionally vomiting. Since spontaneous resolution usually occurs in < 4 days, investigation for the specific organism is only required in:

- Elderly patients, especially those in institutions;
- Immunocompromised patients;
- Symptoms > 5 days;
- Epidemics.

Causes

See Table 5.4.

History

- **History of ingesting suspicious food**:
  - Incubation 1–6 h: *Bacillus cereus*, *Staphylococcus aureus*;
  - Incubation 8–18 h: *Shigella*, *E. coli*, *Campylobacter*, *Clostridium perfringens*;
  - Incubation 12–36 h: *Salmonella*, *Clostridium botulinum*.
- **Diarrhoea**, all organisms cause diarrhoea, bloody in *Shigella*, enterotoxic *E. coli*, *Campylobacter*.
- **Abdominal pain**, *especi*ally in *Campylobacter*.
- **Vomiting**, *es*pecially in *Bacillus cereus* and *Staphylococcus aureus*.
- **Systemic features**, especially in *Shigella*, *Campylobacter*, *Yersinia*.

Table 5.3 Diagnostic methods to detect *Helicobacter pylori*.

	Serology (IgG)	Urea breath test	Faecal antigen test	Urease (CLO) test	Histology	Bacterial culture
Advantages	Specific Quick Useful for screening	Specific and sensitive	Specific and sensitive Cheap	Specific Quick Cheap	Specific and sensitive	'Gold standard' Can test antibiotic sensitivity
Disadvantages	No use to test eradication (IgG) False negatives in older people Need to stop PPIs, antibiotics 4 weeks	Need to stop PPIs, antibiotics 4 weeks Requires radiation or mass spectrometer Slow	Poor acceptability As for serology IgG	Insensitive Need to stop PPIs, antibiotics 4 weeks	Slow Need to stop PPIs, antibiotics 4 weeks	Slow Insensitive Need to stop PPIs, antibiotics 4 weeks

PPI, proton pump inhibitor.

Table 5.4 Infectious causes of acute diarrhoea.

Virus	Norovirus* Rotavirus*
Bacteria	*Salmonella* *Shigella* *Esherichia coli* *Campylobacter* *Yersinia* *Clostridium perfringens*
Bacterial toxins	*E. coli* *Shigella* *Clostridium difficile* *Staphylococcus aureus* *Clostridium botulinum* *Vibrio cholera* *Bacillus cereus*
Protozoa	*Giardia lamblia* *Cryptosporidium* *Cyclospora*

*Commonest causes.

Potential consequences

These occur rarely, but are classical:

- **Chronic diarrhoea**:
  - Post-infectious IBS (see p. 100);
  - Persistent infection (immunosuppressed, *Giardia*);
  - Secondary hypolactasia (especially in children, Asian origin).
- **Reactive arthritis**:
  - May follow *Salmonella* or *Shigella*.
- **Reiter's syndrome** (asymmetrical polyarthritis, conjunctivitis, orogenital mucosal ulceration):
  - May follow *Yersinia* or *Campylobacter*.
- **Erythema nodosum**:
  - May follow *Yersinia* or *Campylobacter*.
- **Toxic megacolon**:
  - Especially with *Clostridium difficile*, *Yersinia*, *Campylobacter*, *E. coli*;
  - More often relates to undiagnosed ulcerative colitis complicated by infection.
- **Asymptomatic carrier state** (*Salmonella*).

Investigations

- Stool culture and microscopy: for cysts and trophozoites.
- Serology for toxins:
  - *C. difficile*;
  - *E. coli*;
  - *Shigella*;
  - *Campylobacter*.
- Sigmoidoscopy and biopsy only indicated if symptoms persist > 2 weeks.
- Joint X-rays and aspiration if joint is swollen and there is fever and leucocytosis.

Management

- **General supportive treatment**:
  - Resuscitation: oral rehydration solution is preferred to IV rehydration, if patient is not vomiting;
  - Meticulous hand hygiene;
  - Antidiarrhoeals (loperamide) should be avoided in most cases, especially in children (when fatal paralytic ileus may occur);
  - Antiemetics may be used more liberally;
  - Food poisoning is a notifiable disease.
- **Specific treatment**:
  - Viruses:
    - Typically self-limiting within 5 days, but may be fatal in elderly and immunocompromised – especially norovirus;
    - Epidemics occur in hospitals and institutions – through uncooked food and hand-to-hand transmission;
    - Supportive treatment only is needed.
  - *Salmonella*:
    - Antibiotic therapy is avoided, as it prolongs gallbladder carriage of the organism;
    - Ciprofloxacin is the first-choice antibiotic, trimethoprim being the alternative;
    - Asymptomatic carriers need no specific management other than advice about good hand hygiene.
  - *Shigella*:
    - If antibiotics are needed, ciprofloxacin is preferred.
  - *E. coli*:
    - Occurs in outbreaks, usually from infected meat;
    - Ciprofloxacin is the first-choice antibiotic, but increases the risk of developing haemolytic uraemic syndrome (due to toxin release).
  - *Campylobacter*:
    - If symptoms persist, ciprofloxacin or erythromycin may be used.
  - *Yersinia*:
    - Diagnosis requires stool culture or elevated antibodies on serology;

  - Tetracycline for 2 weeks is the first-choice antibiotic.
- *C. difficile*:
  - This is a Gram-positive anaerobe that is found everywhere, with 2% of the population being asymptomatic carriers;
  - In hospitals the spores are resistant to most disinfectants;
  - Spectrum of infection occurs, from:
    Asymptomatic carriage, to
    Isolated diarrhoea, to
    Pseudo-membranous colitis (based on endoscopic appearance of a grey 'membrane' overlying colonic mucosa), to
    Death.
  - Risk factors:
    Antibiotics: high risk – cephalosporins, clindamycin; medium risk – penicillins, co-trimoxazole, macrolides; low-risk – metronidazole, vancomycin, metronidazole, ciprofloxacin, aminoglycosides;
    Old age or immunocompromise;
    Concommitant chemotherapy or proton pump inhibitor (PPI).
  - Diagnosis: *C. difficile* toxins A (95%) and B (5%);
  - Management:
    Stop causative antibiotic and *avoid* antidiarrhoeals
    Careful nursing and hand hygiene
    Oral metronidazole for 7–10 days
    Oral (*not* IV) vancomycin for 14–28 days
    Role of probiotics and faecal bacteriotherapy are under investigation for this common hospital condition.
  - Prognosis: 30% mortality in hospital patients.
- *Listeria monocytogenes*:
  - Usually ingested in unpasteurised products;
  - Caution required in immunocompromised and pregnant women where there is significant mortality and risk to the fetus.
- *Giardia*:
  - Chronic infection is a significant potential problem;
  - Course of metronidazole or single-dose tinidazole will usually eradicate the protozoa.
- *Cryptosporidium*:
  - Supportive treatment only is needed as it is self-limiting;
  - Immunocompromised may require azithromycin.
- *Cyclospora*:
  - Common cause of chronic diarrhoea in returning travellers;
  - Responds to a course of co-trimoxazole.

Intestinal tuberculosis

Mycobacterium tuberculosis or *bovis* may cause intestinal infection by:

- Ingestion of infected milk;
- Blood-borne spread from the lung;
- Rarely, direct spread from adjacent organs.

It affects the immigrant population (sub-Saharan Africa, South-East Asia), especially, often many years after arriving in the host country. The malnourished, immunocompromised and institutionalised are also at particular risk.

The differential diagnosis is with Crohn's disease and *Yersinia* infection.

Clinical features

- **Ileocaecal disease** (commonest):
  - Diarrhoea, abdominal pain, weight loss and systemic ill health;
  - Rarely, presentation is with an acute abdomen (TB appendicitis, obstruction or perforation);
  - An abdominal mass is often present.
- **TB adenitis**:
  - Mimics appendicitis.
- **TB peritonitis**:
  - Weight loss, systemic ill health and ascites (diagnosis is established by staining and culture of paracentesed ascites).

Investigations

- Standard TB investigations are often unhelpful: two-thirds of patients will have a normal chest X-ray, and Mantoux testing is poorly sensitive for current infection.
- Tissue diagnosis is required, and also helps with determining drug sensitivity:
  - Ascites: exudate with increased lymphocytes, supported by Ziehl–Nielsen staining and culture of acid-fast bacilli;
  - Peritoneal biopsy, with Abrams' needle or at laparoscopy.

- Abdominal CT or contrast follow-through often reveals features indistinguishable from Crohn's disease (small bowel thickening, intra-abdominal lymphadenopathy, peritoneal reaction).
- Colonoscopy is also indistinguishable from Crohn's disease, but does allow for biopsies to be taken.

Management

- Triple therapy (rifampicin, isonizid and pyrazinamide) for 2 months followed by dual therapy (rifampicin, isonizid) for 4 months.
- Ethambutol may be needed if resistance is suspected.
- Monitoring response: symptoms, weight, ESR, CRP, Hb.
- Monitoring adverse events: liver enzymes.
- Surgery is indicated for:
  - Obstruction;
  - Complications (perforation, haemorrhage);
  - Large abdominal mass (poor antimicrobial penetrance).
- TB is a notifiable disease.

Miscellaneous gut infections

Amoebiasis

- Mostly in immigrant populations, after ingestion of contaminated water or food containing *Entamoeba histolytica*.
- Classically it occurs in patients receiving a course of corticosteroids.
- Usually asymptomatic, but a pancolitis occurs in 10% of those infected, and very rarely a fatal toxic megacolon may occur.
- Rarely, perianal manifestations and fistulisation may occur, resembling Crohn's disease.
- **Diagnosis**:
  - *Entamoeba histolytica* antigen in stool *and* serum; this is preferred to microscopy of warm stool to look for the amoeba. Biopsies may show the flask-shaped mucosal ulceration and trophozoites;
  - One-quarter of patients may develop an amoebic liver abscess (especially men); the risk is of rupture into the peritoneum or pleural cavity;
  - Diagnosis of liver abscess requires imaging (ultrasound or CT) with drainage revealing thick brown ('anchovy sauce') fluid.
- **Management**: metronidazole for 5 days followed by paromyocin to eradicate luminal parasites. Three sequential clear stool samples confirm eradication.

Typhoid and paratyphoid

- Mostly in returning travellers, caused by *Salmonella typhi* or *paratyphi*.
- Symptoms are usually systemic and non-specific (milder in paratyphoid).
- Classic triad is bradycardia, 'rose-spot' rash and constipation (later diarrhoea).
- Hepatosplenomegaly and a leucopaenia are often present.
- Small bowel haemorrhage or perforation occurs in 10%; encephalopathy in 5%.
- **Diagnosis**: usually depends on bone marrow culture (blood culture is only positive in the early stages, when the diagnosis is usually not suspected).
- **Management**: ciprofloxacin or chloramphenicol to eradicate the bacterium, and prednisolone for encephalopathy.

Parasite worm infections

- Roundworm, hookworm, threadworm, whipworm and tapeworm are consumed either by eating contaminated uncooked meat or through the faeco-oral route.
- Infections are usually asymptomatic, but may cause low-grade abdominal distension and nausea. A low-grade anaemia is common with all. Tapeworms are the most likely to give more dramatic symptoms (fever, enterocolitis, cyst formation in brain or muscle, weight loss). There may be pruritus ani or visible worms in the faeces.
- **Diagnosis** is suggested by an eosinophilia, but requires faecal examination for confirmation. Sellotape applied to the anal margin will on examination reveal threadworm, especially common in children.
- **Treatment**: tapeworm requires niclosamide as a stat dose, and the other infections will respond to 3 days of mebendazole or levamisole.

Anal infections

Anal warts

Human papilloma virus (HPV) is the commonest sexually-transmitted virus, and is highly contagious. The warts are frequently multiple with a characteristic cauliflower appearance, and may extend to the dentate line.

Treatment is usually with a topical antiviral (such as podophyllin, podofilox or imiquimod). Alternatively, destructive local therapies such as laser, cryotherapy or electrocoagulation may be considered. Surgery is reserved for large clusters of lesions or when there is extension into the rectum.

Chlamydia

This is the commonest sexually-transmitted disease in the developed world, affecting women slightly more often than men. Urethral discharge and dysuria precede a shallow ulcer on the penis before the characteristic groin lymphadenopathy occurs. In rare late stages, inflammation of the rectum may occur. Diagnosis is based on antibody and complement fixation testing, only occasionally needing histology. Treatment is with azithromycin, doxicycline or co-trimoxazole.

Syphilis, gonorrhoea and herpes simplex

These sexually-transmitted infections occur most frequently in those practising anoreceptive intercourse. Treatment is along standard lines.

Gut symptoms in HIV infection

Any part of the GI tract may be affected in patients with HIV infection; opportunistic gut infections should raise the suspicion of AIDS in these patients. Any of the preceding infections may occur, but specific symptom patterns suggest specific opportunistic infections:

- **Oral ulceration**: herpes simplex, *Candida*, *Neisseria gonorrhoea*, syphilis.
- **Dysphagia**: cytomegalovirus (CMV; see below), *Candida*;
- **Abdominal pain**: TB, CMV in the gallbladder (intestinal lymphoma, Kaposi's sarcoma);
- **Diarrhoea**: TB, *Giardia*, *Cryptosporidium*, *Cyclospora*, *Chlamydia*, CMV, herpes simplex;
- **Rectal stricture**: – *Chlamydia*, lymphogranuloma venereum;
- **Rectal bleeding**: lymphogranuloma venereum, syphilis, (anal cancer, Kaposi's sarcoma).

Cytomegalovirus

CMV can invade the mucosa of any region of the gut, causing symptoms (see above). Histology is diagnostic, showing *multiple* intranuclear inclusion bodies. CMV infection of the colon can occur in any immunocompromised patient, not just those with AIDS; specifically also in patients with a flare-up of ulcerative colitis who have received immunosuppression (prednisolone, azathioprine). Since viraemia is fatal, aggressive treatment may be needed, with intravenous ganciclovir or foscarnet.

6

Gastrointestinal investigations

Structural tests

Radiology

Plain X-rays

- Erect chest X-ray: free air under the diaphragm = perforation.
- Abdominal X-ray:
  - Dilated bowel loops and fluid level = obstruction or ileus;
  - Calcification:
    - Chronic pancreatitis;
    - Gallstones (only 10% radio-opaque).

Contrast studies

The principle is to provide radio-opaque contrast using an insoluble salt (such as barium sulphate) or water-soluble medium (gastrografin); the mucosal images can be enhanced by the double-contrast technique (with co-inflation of gas and contrast). These are real-time studies, so as well as showing mucosal detail, they also give *some* information about gut motility.

Contrast swallow

- **Indications**:
  - Dysphagia (where upper GI endoscopy may be dangerous due to pharyngeal pouch);
  - Suspected dysmotility (where upper GI endoscopy is unhelpful);
  - Size of hiatus hernia (if not quantified at upper GI endoscopy);
  - (Other – heartburn, chest pain).
- **Limitations**:
  - Upper GI endoscopy shows better mucosal detail and allows biopsy;Aspiration risk.

Contrast meal (usually barium)

- **Indications**:
  - Epigastric pain with 'normal' upper GI endoscopy; possible linitis plastic;
  - Vomiting with 'normal' upper GI endoscopy; possible gastric outlet obstruction or dysmotility;
  - Suspected perforation (water-soluble medium);
  - (Anaemia – superseded by capsule endoscopy).
- **Limitations**:
  - Upper GI endoscopy shows better mucosal detail and allows biopsy;
  - Poor at detecting early cancer.

Contrast follow-through

- **Indications**:
  - Crohn's disease: suspected or to quantify extent;
  - Diarrhoea or abdominal pain with normal endoscopy and histology;
  - Suspected small bowel obstruction.
- **Limitations**:
  - Ionising radiation exposure;
  - Expertise dependent.

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Contrast enema

- **Indications**:
  - Altered bowel habit;
  - Suspected diverticulosis where colonoscopy may be difficult or dangerous;
  - Suspected megacolon (where lower GI endoscopy can give false negatives);
  - (Anaemia or rectal bleeding).
- **Limitations**:
  - Uncomfortable for patient;
  - Does not visualise rectal mucosa well (especially if patient is unable to retain contrast due to incontinence);
  - Ionising radiation exposure;
  - Compared to colonoscopy, poor mucosal definition, and cannot biopsy lesions and same bowel preparation required.

Ultrasound

- **Indications**:
  - Abdominal masses: tumour, abscess, cyst;
  - Organomegaly;
  - Jaundice;
  - Gallstones;
  - Biliary tract dilatation;
  - Ascites;
  - Guided procedures (liver biopsy, cyst aspiration, stent insertion).
- **Limitations**:
  - Low sensitivity for lesions <5 mm;
  - Poor views if obstructed (gas) or obese;
  - Expertise dependent;
  - Poor for imaging retroperitoneal structures.

CT scanning

Oral contrast helps mucosal definition; intravenous contrast shows vascular lesions.

- **Indications**:
  - Tumour staging (colorectal, gastric, etc.);
  - Crohn's disease;
  - Pancreatic disease;
  - Bile duct stones (better than ultrasound);
  - Hepatic tumour staging;
  - Guided procedures (cyst aspiration, stent insertion);
  - CT colonography (non-invasive colonic imaging, but requires full bowel prep, and may miss lesions <1 cm).
- **Limitations**:
  - Ionising radiation exposure;
  - May 'under-stage' tumours;
  - Expertise dependent.

MRI scanning

- **Indications**:
  - Tumour staging (especially oesophagogastric);
  - Crohn's disease (small bowel and perianal);
  - Suspected neuroendocrine tumours;
  - Suspected chronic pancreatitis (secretin-stimulated MR);
  - Hepatic tumour staging;
  - MR cholangiopancreatography (MRCP).
- **Limitations**:
  - Expertise dependent;
  - Claustrophobia for some patients;
  - Time consuming;
  - Not feasible if metal prostheses *in situ*.

Mesenteric angiography

- **Indications**:
  - GI haemorrhage with normal upper and lower GI endoscopy;
  - Recurrent iron deficiency;
  - Suspected arterio-venous malformation;
  - Suspected mesenteric ischaemia.
- **Limitations**:
  - Contrast-induced nephropathy;
  - Requires sufficiently brisk bleeding to document source.

Endoscopy

Video-endoscopy enables passage of flexible instruments into the upper and lower extremes of the gut, allowing both direct visualisation of the mucosa and biopsy or procedural interventions.

Upper GI endoscopy

Performed under sedation with intravenous benzodiazepine, or local anaesthetic throat spray only. Should be avoided if perforation is suspected; also caution following recent myocardial infarction or if suspected atlantoaxial subluxation (e.g. rheumatoid arthritis).

- **Indications – diagnostic**:
  - Abdominal pain;
  - Haematemesis or melaena;
  - Dysphagia;
  - Weight loss;

  - Iron-deficiency anaemia (necessitates distal duodenal biopsy);
  - Vomiting;
  - Biopsy of upper GI tract following radiology procedure;
  - Gastric ulcer follow-up;
  - Balloon enteroscopy: an invasive technique allowing visualisation of distal duodenum and jejunum in cases of suspected bleeding or pain of intestinal origin.
- **Indications – therapeutic**:
  - Endoscopic treatment of oesophageal varices;
  - Dilatation of stricture;
  - Insertion of stent to palliate strictures;
  - Placement of PEG tube.
- **Complications**:
  - Perforation (0.1%);
  - Over-sedation resulting in respiratory depression (0.01%);
  - Aspiration pneumonia (avoidable with good nursing assistance and aspiration).

Flexible sigmoidoscopy

Performed without sedation following enema; only the left colon and rectum are examined.

- **Indications**:
  - Fresh rectal bleeding;
  - Quantify activity in known ulcerative colitis patient.
- **Complications** of perforation and haemorrhage are extremely rare.

Colonoscopy

Performed after full bowel preparation and with conscious sedation; the entire colon (and if possible the terminal ileum) are examined.

- **Indications – diagnostic**:
  - Altered bowel habit (constipation or diarrhoea);
  - Rectal bleeding;
  - Iron-deficiency anaemia;
  - Suspected inflammatory bowel disease;
  - Follow-up of abnormal barium enema;
  - Colorectal cancer screening;
  - Surveillance:
    - Post-colectomy for cancer;
    - For adenoma;
    - For inflammatory bowel disease.
- **Indications – therapeutic**:
  - Polypectomy;
  - Argon or laser photocoagulation of vascular lesion;
  - Dilatation or stent insertion.
- **Complications**:
  - Incomplete examination (10%), depending on expertise;
  - Perforation (0.5% therapeutic procedures, 0.1% diagnostic ones);
  - Haemorrhage (half the perforation rate);
  - Cardiorespiratory depression if over-sedated;
  - Infective endocarditis (avoidable with prophylactic antibiotics in at-risk patients, i.e. those with previous endocarditis or prophylactic heart valves).

Endoscopic ultrasound

Performed with specialised endoscopes, bearing a revolving ultrasonic probe at the tip of the 'scope.

- **Indications**:
  - Staging of cancers of oesophagus, rectum and pancreas;
  - Drainage of pancreatic pseudocysts;
  - Lymph node biopsy;
  - Assessment of anal sphincters in faecal incontinence.

Video-capsule enteroscopy

Allows visualisation of distal small bowel by a swallowed disposable video-capsule.

- **Indications**:
  - Obscure GI bleeding;
  - Recurrent anaemia.
- **Limitations**:
  - Caution required if strictures are suspected, as the capsule can then obstruct;
  - Expense.

Radioisotope studies

Meckel's scan

- Technetium (^{99m}Tc) is selectively taken up by parietal cells;
- Thus, intravenous infusion of labelled ^{99m}Tc allows localisation of ectopic tissue in a **Meckel's diverticulum**.

Labelled white cell scan

- Patient's own leucocytes are extracted and radiolabelled before being reintroduced;

- Thus, they migrate to sites of infection or inflammation (Crohn's disease) which can now be localised.

Labelled red cell scan

- Patient's own erythrocytes are extracted and radiolabelled before being reintroduced;
- Thus, they can be seen as they are extravasated from the gut.

Bile acid absorption test

- Radiolabelled bile acid substrate is consumed orally, and should be absorbed and stored as ^{75}SeHCAT;
- Test allows quantification of the amount that is retained after 7 days, with anything <5% retention being abnormal.

Physiological tests

Gut hormone analysis

Performed to assess secretory diarrhoea or suspected Zollinger–Ellison syndrome. Requires cessation of proton pump inhibitor (PPI) for 2 weeks. Results are of the fasting levels of:

- Gastrin;
- Glucagon;
- Vasoactive intestinal polypeptide (VIP);
- Pancreatic polypeptide;
- Somatostatin;
- Calcitonin.

Breath tests

These depend on the following simple principle:

Substrate + Physiological **or** Pathological host factor → Physiological metabolite(s) + Gas by-product

For each test, the principle is exploited to measure a lack or excess of the host factor. The methodology for each test is that the substrate is given and gas samples are collected regularly for 120 min.

Lactose hydrogen breath test

To diagnose hypolactasia ('lactose intolerance').

- Substrate = lactose.
- Host factor = brush border lactase levels (physiological).
- Physiological metabolites = glucose and galactose.
- Gas by-products = nil:
  - In hypolactasia, the lactose is not digested and so enters the colon, where it is metabolised by bacteria-releasing hydrogen;
  - Positive result is an elevated breath hydrogen sooner than 120 min (i.e. when lactose substrate has reached the colon).

Glucose (or lactulose) hydrogen breath test

To diagnose small intestine bacterial overgrowth.

- Substrate = glucose (or lactulose).
- Host factor = bacteria present in small intestine (pathological).
- Physiological metabolite = energy.
- Gas by-product = hydrogen:
  - In bacterial overgrowth, the flora in the small intestine digest the glucose-releasing hydrogen;
  - Positive result is an elevated breath hydrogen sooner than 60 min (i.e. well before substrate has reached colonic flora).

^{14}C-xylose carbon dioxide breath test

To diagnose small intestine bacterial overgrowth.

- Substrate = ^{14}C-xylose.
- Host factor = bacteria present in small intestine (pathological).
- Physiological metabolite = energy.
- Gas by-product = carbon dioxide:
  - In bacterial overgrowth, the flora in the small intestine digest the xylose-releasing $^{14}CO_2$;
  - Positive result is an elevated breath $^{14}CO_2$ sooner than 60 min (i.e. well before substrate has reached colonic flora).

^{14}C-triolein carbon dioxide breath test

To diagnose fat malabsorption.

- Substrate = ^{14}C-triolein (a triglyceride).
- Host factor = lipase enzymes (physiological).
- Physiological metabolite = oleic acid.
- Gas by-product = carbon dioxide:
  - In fat malabsorption, there is less hydrolysis of the triolein substrate, hence less oleic acid produced, hence less $^{14}CO_2$;

- Positive result is a reduced breath $^{14}CO_2$ sooner than 60 min (i.e. well before substrate has reached colonic flora).

^{14}C- or ^{13}C-urea carbon dioxide breath test

To identify the presence of *Helicobacter pylori* (especially to confirm eradication in those who have been treated but have persistent or recurrent symptoms).

- Substrate = ^{14}C- or ^{13}C-urea.
- Host factor = *Helicobacter pylori* (pathological).
- Physiological metabolite = ammonium.
- Gas by-product = carbon dioxide:
  - In *Helicobacter pylori* infection there is increased cleavage of urea by the bacteria (which possess the enzyme urease), and hence an increase of CO_2;
  - Positive result is an elevated breath $^{14}CO_2$ or $^{13}CO_2$ at 20 min.

Mucosal inflammation tests

Intestine permeability studies

- **Principle**: the normal small bowel absorbs mono-, not di-, saccharides. Once absorbed they are excreted in the urine. An increase in permeability allows both mono- and di-saccharides to be absorbed.
- **Method**: oral lactulose and rhamnose are ingested, before accurate urinary measurement of the sugars, expressed as a ratio.
- **Results**: increased permeability in Crohn's disease and coeliac disease.

Faecal calprotectin

- **Principle**: calprotectin is a peptide expressed by colonic neutrophils.
- **Method**: faecal estimation of concentration of calprotectin.
- **Results**: increased levels in colonic inflammation, infections and cancers.

Oesophageal physiology

Stationary manometry (Figure 6.1)

A transnasal catheter is passed into the oesophagus and gives information about:

- Contractions in the body of the oesophagus;
- Function and pressure of the lower oesophageal sphincter (LOS).

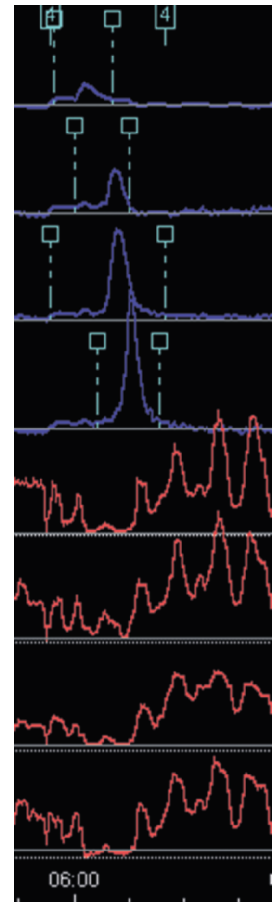

Figure 6.1 Stationary oesophageal manometry trace showing normal peristalsis in upper four graphs and relaxation of lower oesophageal sphincter in lower four graphs. Each horizontal division represents 5 s.

- **Indications**:
  - Suspected achalasia: manometry is the diagnostic test, showing:
    - Absence of peristalsis in body of oesophagus (mandatory);
    - Non-relaxation of the LOS (often);
    - Elevated LOS pressure (occasional);
    - Elevated pressures in body of oesophagus (occasional).
  - Suspected other oesophageal dysmotility (though ambulatory studies may be needed);
  - Prior to proposed antireflux surgery (to exclude dysmotility prior to surgery).

Ambulatory manometry

A transnasal catheter is placed in the oesophagus for a 24-h period, measuring contraction patterns whilst the patient continues normal activities.

- **Indication**: Chest pain where coronary artery disease has been excluded (to exclude oesophageal spasm).

Ambulatory pH studies

A transnasal pH catheter is placed in the oesophagus for 24–48 h, allowing:

- Quantification of degree of acid exposure;
- Timing of symptom episodes with objective episodes of reflux into the oesophagus.

- **Indications**:
  - Suspected gastro-oesophageal reflux where endoscopy shows no oesophagitis (to confirm whether there is objective acid reflux);
  - Refractory gastro-oesophageal reflux (to confirm adequacy of acid suppression);
  - Prior to proposed antireflux surgery (to confirm pathological degree of acid reflux).

A recent advance has been ambulatory impedance studies which allow quantification not only of acid reflux, but also of non-acid reflux episodes.

Gastric emptying

In suspected gastroparesis, endoscopy and contrast studies are often normal (with the exception of possibly showing persistence of gastric content despite an adequate period of fasting). The rate of gastric emptying can be accurately quantified using a *radio-isotope-labelled meal*, with different labels on the solid (technetium) and liquid (indium) phase of the test meal. Normal emptying is for 50% of the solid phase to be empty by 90 min.

Whole gut transit

Oroanal transit time in health is highly variable, but approximates to between 20 and 40 h (see p. 20), the majority of that time being spent in the colon. This rate of transit can be assessed by undertaking an abdominal X-ray on day 5 after three sets of distinct *radio-opaque markers ('shapes study')* have been ingested on days 1, 2 and 3. Persistence of excessive numbers of any one of the sets of markers indicates slow transit, and is a valuable test in patients with chronic constipation.

Anorectal physiology

This term refers to a battery of tests undertaken to investigate anorectal function in a laboratory setting. They are complementary to a focused history of bowel function and imaging studies (most commonly endo-anal ultrasound or proctography). Measures are obtained of:

- Anal sphincter pressure;
- Rectal sensitivity and compliance;
- Anorectal reflexes.

- **Indications**:
  - Faecal incontinence;
  - Suspected Hirschsprung's disease (see p. 108);
  - Prior to ileoanal pouch surgery (to confirm sphincter competence).

7

Acute gastrointestinal bleeding

Acute upper gastrointestinal bleeding

Haematemesis (vomiting blood) occurs when the bleeding source is proximal to the jejunum, and **melaena** (tarry stool) usually occurs when blood loss is proximal to the caecum. It is a common cause of inpatient mortality, but outcome very much depends on the expertise available – 5% in the best centres and 20% in others. The aims of management are to:

- Resuscitate the patient;
- Arrest the bleeding;
- Prevent or promptly recognise rebleeding.

Causes (in order of occurrence)

- Peptic ulcer (duodenal > gastric);
- Gastric erosions/gastritis;
- Mallory–Weiss tear;
- Gastro-oesophageal varices (~5% of acute bleeds, but 80% of mortality);
- Duodenitis;
- Oesophagitis;
- Tumours (gastric > oesophageal);
- Gastric antral vascular ectasia (GAVE);
- Dieulafoy lesions;
- Hereditary haemorrhagic telangiectasia;
- Aorto-enteric fistula;
- Clotting defect.

Management – general

- Assess initial Rockall score to predict mortality risk (Table 7.1).
- Initial resuscitation.
- Intravenous access.
- Give colloid (preferred to crystalloid) if hypotensive or tachycardic.
- If Rockall shock score 2, insert central venous catheter and urinary catheter and get a surgical consultation.
- Keep nil by mouth (until endoscopy).
- **Initial investigations**:
  - Check bloods for FBC, renal and liver function, clotting status;
  - If major blood loss, cross-match blood; if not, group and save blood;
  - Arterial blood gases, chest X-ray and ECG if cardiorespiratory disease present;
  - Upper GI endoscopy: best performed on a daytime list, but emergency procedure indicated if there is:
    - High likelihood of variceal bleed (history of or stigmata of chronic liver disease);
    - Rebleeding of a hospital patient;
    - Bleeding after endoscopy;
    - High chance of acute surgery.
- Endoscopic intervention is preferred to surgery for peptic ulcer (thermocoagulation, adrenaline injection, vessel clip) and for varices (see p. 132).
- Endoscopy also permits check of *Helicobacter pylori* status in peptic ulcer patients.
- Assess post-endoscopy Rockall score to predict risk (Table 7.2).

Lecture Notes: Gastroenterology and Hepatology, 1st edition. Anton Emmanuel and Stephen Inns.

Table 7.1 Rockall score – initial.

Criterion		Score
Age	<59	0
	60–79	1
	>80	2
	None	0
	Pulse, BP > 100	1
	BP < 100	2
Comorbidity	None	0
	Cardiac/lung / major	2
	Renal/liver/cancer	3
Total		0–7

Table 7.2 Rockall score – post-endoscopy.

Criterion		Score
Endoscopic diagnosis	Normal, Mallory–Weiss tear	0
	Any other lesion	1
	Upper GI cancer	2
Stigma of recent bleed	None, black spots	0
	Clot, visible vessel, blood in stomach	2
	BP < 10	2
Post-endoscopy sub total		0–4
Total	Add initial score	0–11

Management – specific

Oesophageogastric varices

See p. 132.

Peptic ulcers

See also p. 82.

- Intravenous omeprazole or pantoprazole (halves chance of rebleeding).
- There is no role for ranitidine or oral proton pump inhibitor (PPI).
- Tranexamic acid (an antifibrinolytic) may help reduce bleeding.
- Monitor for rebleeding:
  - Rise in heart rate (most sensitive indicator);
  - Fall in venous pressure or urine output;
  - Overt haematemesis (more sensitive than melaena).
- Liaise with surgical team especially if:
  - Large number of units of blood are being required;
  - There is continued bleeding, or rebleeding, despite endoscopy;
  - A spurting vessel was seen at endoscopy.

Mallory–Weiss tears

- Typical feature is that bleeding is not seen in the initial vomitus;
- Acid suppression not required (>90% heal spontaneously);
- Continued bleeding may, rarely, warrant endoscopic therapy.

Gastric erosions

- Usually related to a combination of NSAIDs, alcohol and stress;
- Treatment is with a PPI for 2–4 weeks;
- Continued bleeding may respond to tranexamic acid.

Aorto-enteric fistula

- Consider in any patient who has had aortic graft surgery and presents with GI blood loss;
- Diagnosis is best made by abdominal CT;
- Management requires surgery rather than endoscopy.

No source of bleeding found

- Most often due to a common lesion missed at upper GI endoscopy, so careful re-examination by an expert is warranted, especially if there is continued bleeding.
- Rarely, other lesions may be the cause:
  - Dieulafoy lesion that has healed by time of endoscopy;
  - Distal duodenal bleeding (NSAID, Zollinger–Ellison peptic ulcers);
  - Meckel's diverticulum.

Acute lower gastrointestinal bleeding

This is distinct from melaena in that blood loss is either red–brown or fresh and bright. Causes are almost invariably due to a colonic or anal source of blood loss; a more useful classification is according to frequency of particular lesions occurring.

Causes (in approximate order of frequency)

- Haemorrhoids: these are so common that they may occur synchronously with other causes;
- Anal fissure;
- Colorectal polyps;
- Colorectal cancer;
- Ulcerative colitis > Crohn's colitis;
- Rectal prolapse;
- Diverticular disease;
- Angiodysplasia;
- Ischaemic colitis;
- Solitary rectal ulcer syndrome with/without rectal prolapse;
- Vasculitis;
- Small intestinal disease (lymphoma, diverticula).

Management

- Initial resuscitation.
- Initial investigation.
- Check bloods for FBC, renal and liver function, clotting status.
- If major blood loss, cross-match blood; if not, group and save blood.
- Prompt lower GI endoscopy:
  - Colonoscopy if altered bleeding;
  - Flexible sigmoidoscopy if fresh rectal bleeding;
  - Upper GI endoscopy is only required if there is major circulatory collapse (when the source may be a rapidly bleeding upper GI lesion causing the presentation).
- Mesenteric angiography is only needed if there is continued heavy bleeding (loss of >1 g Hb/4 h).
- If there is recurrent bleeding and no source has been identified, the following are indicated *in sequence*:
  1. Repeat colonoscopy by an expert; *if nil found, go to 2*;
  2. Barium small bowel enema or follow through; *if nil found, go to 3*;
  3. Video-capsule enteroscopy; *if nil found, consider 4 or 5*;
  4. Meckel's scan; *or*
  5. Red cell scan.
- In most cases, spontaneous cessation of bleeding occurs. However:
  - If blood loss continues from an identified source, consideration of surgical resection is reasonable;
  - If blood loss continues from an unidentified source, laparotomy with on-table colonoscopy.

8

Acute upper and lower gastrointestinal emergencies

Gastrointestinal emergency presentations account for a significant proportion of acute presentations to the A&E department – both to surgeons and physicians. The potential presentations are listed anatomically in this section. Presentations with isolated acute abdominal pain are covered in Chapter 3.

Acute total dysphagia

Sudden complete dysphagia for solids and liquids is a medical emergency requiring instant relief of obstruction. The commonest cause is bolus food impaction on a pre-existing lesion (cancer, benign stricture, web). The dangers relate to the risk of aspiration pneumonia, and the extreme distress to the patient from not being able to swallow even their saliva.

Management

- Reassurance.
- Rehydration.
- Endoscopic removal of obstruction.
- Endoscopic dilatation of stricture if appropriate; if not, an enteral feeding tube should be placed.
- Treat aspiration pneumonia if appropriate.
- Give advice about avoiding dysphagia:
  - Good dentition and careful mastication;
  - Avoid fibrous foods;
  - Plentiful drinks, especially carbonated;
  - Proton pump inhibitor (PPI) if stricture present.

Lecture Notes: Gastroenterology and Hepatology, 1st edition. Anton Emmanuel and Stephen Inns.

Oesophageal rupture

Sudden severe chest pain after an obvious provoking cause. In order of frequency, causes are:

- Endoscopy or other instrumentation (usually small tears);
- Chest trauma;
- Forceful severe vomiting (usually large tears).

The differential includes myocardial infarction, dissecting aneurysm, acute pancreatitis, gastrointestinal perforation.

Investigations

Investigations are therefore driven towards confirming the condition, excluding the differential diagnosis (see below in parenthesis), identifying the site of perforation and identifying complications:

- ECG and cardiac enzymes (MI);
- Erect chest X-ray (dissecting aneurysm, perforated viscus, pneumothorax),
- will also show surgical and mediastinal emphysema, and possibly a pleural effusion as a complication of the rupture;

- CT scan chest and abdomen (dissecting aneurysm, perforated viscus);
- Serum amylase (acute pancreatitis >> perforated viscus);
- Gastrografin swallow: to confirm location.

Management

- Analgesia (potent);
- Intravenous fluids and keep nil by mouth;
- Urgent surgical opinion.

Large tears (based on gastrografin swallow) and spontaneous ruptures

- Intravenous antibiotics (metronidazole and broad-spectrum agent);
- *Early* surgical repair;
- Enteral nutrition (via jejunal feeding tube).

Small tears

- Conservative management (and operate if fever or pneumothorax develops);
- If rupture complicates oesophageal malignancy, a cuffed oesophageal tube can be placed to palliate.

Acute diarrhoea

The presentation and causes of acute diarrhoea are detailed on p. 42.

Management

Fluid replacement

- Oral replacement is sufficient in most cases.
- Isotonic fluid is required to replace diarrhoeal losses (which are isotonic themselves).
- Glucose is required to drive mucosal absorption of the ions in this isotonic fluid.
- This combination of isotonic fluid and glucose is found in oral rehydration solutions (ORSs).
- A few figures:
  - Adults lose 1 l for every 24 h with moderate diarrhoea (6–8 stools/day);
  - Typically 200 ml of isotonic fluid is lost with each stool;
  - One sachet of commercial oral rehy dration solution provides 200 ml of isotonic fluid;
  - Fluid replacement of diarrhoea as per above needs to *supplement* the minimum 1.5 l of liquid that an adult needs per day.

Antibiotic therapy

- Antimicrobials are not usually indicated since acute infections typically last only 1–3 days (in addition to the risks of antibiotic-related diarrhoea and emerging antibiotic resistance).
- Antibiotics are indicated in certain patient groups (see p. 42).
- Antibiotics are also indicated in epidemic diarrhoea, in order to control spread of infection.

Antidiarrhoeal therapy

These agents are best avoided as they may prolong carriage of the organism, and as such they are absolutely contraindicated in cases of bloody diarrhoea (where an enteroinvasive organism may be causative). They may trigger intususception or ileus in children.

Gut obstruction and ileus

History

The history of the symptoms preceding intestinal obstruction gives invaluable clues as to the location and cause (Table 8.1). In the patient with a past history of laparotomy and sudden onset of central abdominal pain and vomiting, adhesional obstruction of the small bowel is most likely. Patients with obstruction within hernia may give a history of a pre-existing hernia: usually inguinal or incisional. More chronic progressive presentations suggest an inflammatory or malignant cause of obstruction.

Proximal obstruction is associated with marked vomiting and pain, but not usually abdominal distension. More distal small bowel lesions tend to result in more abdominal distension and less vomiting. Marked unexplainable weight loss suggests a malignant process or a chronic inflammatory disease such as Crohn's disease. Generally, pain caused by small intestinal obstruction is felt in the central abdomen. It may be colicky in nature, waxing and waning over periods of minutes. Severe localised unremitting pain is suggestive of strangulated obstruction.

Table 8.1 Causes of gut obstruction.

Mechanism	Site	Examples
Mechanical	Extrinsic	Intestinal hernia* Adhesions* Volvulus (sigmoid >> caecal >> gastric)
	Mural	Malignancy (carcinoma >> lymphoma > carcinoid)* Diverticular disease Stricturing Crohn's disease NSAID-induced strictures Radiation enterocolitis Intestinal tuberculosis
	Luminal	Foreign body Bezoar (food bolus) Intussusception Gallstone ileus
Paralytic ('ileus')	Multiple sites	Postoperative* Chronic intestinal pseudo-obstruction Intestinal ischaemia
	Retro-peritoneal	Pancreatitis Tumours (sarcoma) Retro-peritoneal fibrosis
	Metabolic	Hypokalaemia Diabetic ketoacidosis Acute renal failure

*Commonest causes.

Colonic lesions on the left side may be associated with rectal bleeding or a change in the stool calibre. There may be difficulty with evacuation but if the lesion allows passage of fluid stool only, there may be pseudo-diarrhoea. Pain from colonic obstruction tends to be felt peri-umbilically and in the hypogastrium.

Examination

On general observation the patient may be in obvious pain and/or vomiting. The nutritional status should be assessed. The abdomen, including the inguinal regions, must be carefully examined for the presence of hernias. Tenderness may be generalised and will not necessarily aid localisation of the lesion. Bowel sounds may be high pitched where an overactive small bowel attempts to push luminal substrate through a narrow opening. They may be absent in established obstruction. Peritonism occurs where the viscus has perforated. Rectal examination must always be performed in order to rule out palpable rectal lesions, establish whether there is stool in the rectum and to detect left-sided colonic bleeding.

Management – general

- **Initial resuscitation**:
  - Intravenous access;
  - Give crystalloid, including potassium;
  - Insert nasogastric suction tube;
  - Keep nil by mouth (until endoscopy).
- **Initial investigations**:
  - Plain abdominal X-ray: supine and erect; look for:
    - Gas distribution: valvulae conniventes (traverse the full width of the small intestine) or haustra (partially traverse the width of the colon);
    - Fluid levels;
    - Luminal dilatation;
    - Mucosal oedema.
  - Erect chest X-ray: look for air under the diaphragm;
  - Check bloods:

Table 8.2 Symptoms, investigation and management of gut obstruction according to site of obstruction.

Site of obstruction	Common causes	Typical symptoms	Diagnosis	Management options
Oesophagus	Malignancy	Progressive difficulty swallowing, particularly 'hard' foods	Upper GI endoscopy	Dependent on stage and grade (see Chapter 28) Palliation: • Endoluminal stent • Radiotherapy laser therapy Curative: • Surgery • Radiotherapy
	Peptic stricture	Frequently past history of reflux symptoms Slowly progressive dysphagia to solids	Upper GI endoscopy	Endoscopic dilatation followed by PPI long term
	Food bolus obstruction Foreign body	Sudden onset of pain and dysphagia Unable to swallow saliva	Plain X-ray if foreign body Upper GI endoscopy	Endoscopic removal Rule out underlying lesion in food bolus obstruction
Stomach	Pyloric stenosis (related to peptic ulcer disease in adults)	Slowly progressive	Upper GI endoscopy	Surgical pyloroplasty Endoscopic dilatation
	Gastric cancer	Progressive postprandial vomiting and upper abdominal bloating Cachexia	Upper GI endoscopy	
	Gastroparesis	Intermittent nausea and vomiting Association with diabetes mellitus	Scintigraphic meal to estimate gastric emptying half time Upper GI endoscopy shows no outlet obstruction but may show large gastric residue	Careful diabetic control Prokinetics (gastric pacing)
Duodenum	Pancreatic cancer	Progressive pain, nausea and vomiting Cachexia	CT abdomen Upper GI endoscopy ERCP	Curative: • Whipple's procedure Palliative: • Endoluminal stent • Surgical bypass
Jejunum and ileum	Benign extrinsic obstruction • Adhesions • Hernia	Sudden onset of pain, nausea and vomiting Abdominal distension depending on site	Small bowel radiology, particularly enteroclysis	Surgical management

Table 8.2 *Continued*

Site of obstruction	Common causes	Typical symptoms	Diagnosis	Management options
	Crohn's stricture	Diarrhoea Malabsorption Relapsing and remitting symptoms	Small bowel radiology • Enteroclysis • MRI • Ultrasound Colonoscopy and ileoscopy Enteroscopy Capsule endoscopy (risk of capsule retention)	Medical therapy of Crohn's disease Surgical resection or stricturoplasty Endoscopic dilatation of ileocaecal valve and terminal ileal strictures
	Small bowel carcinoma and lymphoma	Progressive nausea, vomiting and bloating	Small bowel radiology CT abdomen	Surgical resection with or without chemotherapy
	Meckel's diverticulum	History of occult GI bleeding in some	Small bowel radiology Meckel's scan	Surgical resection
Colon and rectum	Colorectal carcinoma	Rectal bleeding and change in stool form with left-sided lesions Cachexia	Colonoscopy CT colonography Barium enema	Surgical excision with or without chemotherapy Endoluminal stenting or ostomy formation for palliation
	Benign stricture • Diverticular • Crohn's disease		Colonoscopy CT colonography Barium enema	Medical therapy of Crohn's disease Surgical resection Endoscopic dilatation in Crohn's disease
	Extrinsic compression • Uterine cancer • Ovarian carcinoma • Lymphoma		CT abdomen Colonoscopy Barium enema	Surgical or other treatment of underlying lesion Endoluminal stenting for palliation
	Sigmoid volvulus	Constipation, abdominal distension	Plain X-ray or gastrografin enema	Flatus tube, endoscopic deflation or surgical resection
	Foreign body insertion		Plain X-ray Rigid or flexible sigmoidoscopy	Per anal or surgical extraction

ERCP, endoscopic retrograde cholangiopancreatography.

    - For FBC: increased white cell count suggests strangulation;
    - Renal and liver function: hypokalaemia and increased urea are found in ileus.
  - Abdominal CT scan: this is the most useful examination to determine site and cause of obstruction;
  - Arterial blood gases: severe vomiting causes metabolic alkalosis.
- If there is strangulation (fever, rebound tenderness and increased white count), then surgery is required.
- Monitor:
  - Hydration status (venous pressure, signs of hydration);
  - Nasogastric aspirate volume;
  - Urine output;
  - Electrolyte status.

Management – specific (Table 8.2)

- **Paralytic ileus**:
  - Stop provoking drugs (anticholinergics) and minimise opiate analgaesia;
  - Give crystalloid, including potassium;
  - Meticulous attention to hydration and serum potassium;
  - Consider domperidone, metoclopramide or erythromycin (prokinetics);
  - Consider parenteral nutrition if prolonged.
- **Intususception**:
  - Diagnosis is often established by ultrasound;
  - Barium or gastrograffin meal may be therapeutic in reducing intussusception.
- **Meckel's diverticulum**: treat surgically if that is the cause.
- **Volvulus**:
  - Sigmoid: deflating the gut (flatus tube or colonoscopy) is preferable to surgery;
  - Caecal: recurrence is frequent, so surgery is advised;
  - Gastric: surgery to reduce the volvulus and repair diaphragmatic hiatus that allows the gastric volvulus.

Foreign bodies

In the case of swallowed foreign bodies, the priority is to safeguard the airway. If the object is impacted in the pharynx, or is likely to become so on attempted removal, then an ENT surgeon should be available. Once past the pylorus, spontaneous anal passage is the norm, though rarely perforation at the ileo-caecal valve may occur. Severe pain and fever should raise the concern of perforation.

Management

- Reassure the patient.
- Perform chest and abdominal X-rays to confirm nature and quantity of ingested item (normal X-rays do not exclude the diagnosis):
  - Sharp items and batteries:
    - If within the oesophagus or stomach, remove at endoscopy (an overtube is needed to protect the pharynx on extubation);
    - If past the pylorus, commence watchful waiting.
  - Blunt items and coins: watchful waiting, as most will spontaneously pass;
  - Smuggled drug packets:
    - Surgical removal is preferred to endoscopic (due to risk of rupture);
    - Monitor for risks of overdose in case of rupture.
  - Rectal foreign bodies:
    - Usually need surgical removal at examination under anaesthetic;
    - Treat the patient with dignity;
    - Consider psychiatric referral as appropriate.

9

Acute liver failure

Acute failure of liver synthetic and metabolic function in the presence of encephalopathy and the absence of pre-existing liver disease defines acute liver failure (ALF) and presents the clinician with a particular set of diagnostic and management problems, often requiring the input of a specialist liver service.

The most common causes of death in ALF are:

- Cerebral oedema;
- Infection;
- Multiorgan failure.

The aim of management is to avoid these complications and allow the liver to regenerate. Acute liver transplantation remains the only definitive therapy when supportive care fails.

Pathophysiology

Systemic inflammatory response syndrome and infection

ALF is haemodynamically characterised by a hyperdynamic circulation with high cardiac output and low systemic vascular resistance. The pathophysiological mechanisms underlying these haemodynamic disturbances are unclear, but increased nitric oxide production and cGMP have been demonstrated during the later stages of the disease. These changes can occur in the absence of microbiologically confirmed infection.

More than 80% of ALF patients do develop infection, mostly pulmonary. Patients with ALF are functionally immunosuppressed (related to Kupffer cell and polymorph dysfunction, as well as reduction of fibronectin, opsonins, chemoattractants and components of the complement system). Hence, fever and leucocytosis may not occur in the face of sepsis. The majority of pathogens are Gram-positive organisms, usually staphylococci. Fungal infections, occurring in about a third of patients, are difficult to detect and are associated with a grim prognosis.

Hepatic encephalopathy and raised intracranial pressure

Hepatic encephalopathy and raised intracranial pressure (ICP) progress hand in hand. Initially encephalopathy develops without raised ICP, but as it progresses to grade 3–4 there is a high risk of increased ICP developing (Table 9.1). The pathogenic mechanisms centre on failure of the liver to clear mainly nitrogenous waste from the bloodstream. Worsening encephalopathy is associated with worsening prognosis (see Table 9.2).

Raised ICP can lead to brainstem herniation, which is the commonest cause of death. Putative mechanisms include:

- Accumulation of osmolytes (such as glutamine) in brain cells, and hence uptake of water into the cells;

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Table 9.1 Grading of hepatic encephalopathy.

Grade	Level of consciousness	Personality and intellect	Neurological signs	Electroencephalogram abnormalities
0	Normal	Normal	None	None
Subclinical	Normal	Normal	Abnormalities only on psychometric testing	None
1	Day/night sleep reversal Restlessness	Forgetfulness Mild confusion Agitation Irritability	Tremor Apraxia Inco-ordination Impaired handwriting	Triphasic waves (5 Hz)
2	Lethargy Slowed responses	Disorientation to time Loss of inhibition Inappropriate behaviour	Asterixis Dysarthria Ataxia Hypoactive reflexes	Triphasic waves (5 Hz)
3	Somnolence Confusion	Disorientation to place Aggressive behaviour	Asterixis Muscular rigidity Babinski signs Hyperactive reflexes	Triphasic waves (5 Hz)
4	Coma	None	Decerebration	Delta/slow wave activity

Table 9.2 King's College criteria of poor prognosis in acute liver failure.

	Criterion	Paracetamol- induced ALF	Non-paracetamol- induced ALF
		Either *pH < 7.3* or all of *2, 3 and 4*	Either INR > 6.5 or 3 of the following 5
1	INR	>6.5	>3.5
2	Creatinine	>300 µmol/l (>3.4 mg/dl)	>300 µmol/l (>3.4 mg/dl)
3	Encephalopathy	Grade 3 or 4	
4	Patient age		<11 or >40
5	Days from jaundice to coma		>7 days
6	Drug toxicity		present

- Cerebral blood flow changes: initial decrease due to loss of the autoregulatory mechanisms to maintain perfusion pressure, and then later increase due to inappropriate vasodilation;
- Disruption of the blood–brain barrier with leakage of plasma into the cerebrospinal fluid.

Coagulopathy

Due to the liver's role in the production of coagulation factors, inhibitors of coagulation and components of the fibrinolytic system, as well as the clearance of activated clotting factors, disturbance of its function results in a complex coagulopathy characterised by factor deficiency and intravascular coagulation. The prothrombin time is widely used to assess coagulation and is a useful guide to prognosis.

Renal, electrolyte and metabolic disturbance

Renal impairment is common; 70–80% of those who have cerebral oedema require some form of extracorporeal renal replacement. The aetiology of renal dysfunction is a combination of:

- Effects of liver cell failure itself (hepatorenal syndrome);
- Acute tubular necrosis (related to sepsis, endotoxaemia, bleeding or hypotension).

Because paracetamol has a direct effect on the renal tubule, renal failure is particularly common in the setting of overdose with this agent. Serum creatinine is the preferred indicator of renal function as urea synthesis by the liver will be decreased.

Hypokalaemia develops as a result of renal losses and can be compounded iatrogenically if potassium is not adequately replaced. **Hypophosphataemia**, **hypocalcaemia** and **hypomagnesaemia** also commonly develop. **Hyponatraemia** is usually seen only in the latter stages of disease. **Acidosis** commonly develops because of:

- Inadequate tissue perfusion causing lactic acidosis;
- Respiratory depression or pulmonary complications causing respiratory acidosis.

Acidosis occurs particularly in paracetamol overdose, and is a determinant of prognosis.

Hypoglycaemia occurs in 40% of patients and is due to failure of gluconeogenesis and raised insulin levels because of reduced hepatic uptake. Neuroglycopaenia can contribute to reduced consciousness.

Evaluation

History

Obtaining an accurate history can be very difficult when faced with an encephalopathic patient. Appropriate third-party information must be obtained, both to guide diagnostic thinking and to decide on the appropriateness of possible liver transplantation:

- Onset and duration of the disease;
- Propensity for, or known, pre-existing liver disease (focusing on alcohol and drug consumption, both prescription and illicit);
- Patient's social context;
- Premorbid function and social support networks.

The time between onset of the first symptoms of illness and hepatic encephalopathy divides the illness into hyperacute (within 7 days), acute (between 8 and 28 days) and subacute (>28 days) subgroups. In the hyperacute subgroup, the prognosis is better than for those with acute or subacute disease.

The features prior to onset of jaundice are non-specific, including nausea and malaise. Vomiting is common but abdominal pain rare. Jaundice *precedes* the onset of hepatic encephalopathy. Coma may then develop rapidly within a few days.

Rarer pathogens should be sought if there is no drug or alcohol history, including plant substances, and potential infectious exposures. It is important to recall the time delay of 2–3 days between paracetamol overdose and liver damage.

Worldwide, viral infection, and in the developed world, paracetamol overdose and idiosyncratic drug reactions, are by far the commonest causes (Box 9.1). However, the list of possible differential diagnoses is long and when an alternative diagnosis seems likely, historical features should guide investigation. In up to 15% of cases no cause will be found.

Examination

Differentiation of ALF from acute on chronic disease is aided by careful observation for the stigmata of chronic liver disease, in particular the presence of a hard liver, marked splenomegaly and spider naevi.

Investigations

Prognostic tests (Table 9.2)

The first task for the clinician is to select those patients with ALF most likely to require transfer to a specialist liver unit. Once under the care of a transplant unit, criteria have been defined that allow the selection of candidates appropriate for transplantation:

- **A**rterial blood gas measurement (especially in paracetamol overdose);
- **B**ilirubin;
- **C**oagulation studies;
- Thrombocytopaenia (secondary to **d**isseminated intravascular coagulation).

Additional tests

- While the transaminases are of little prognostic value, a low albumin indicates poor prognosis.

Box 9.1 Causes of acute liver failure.

Viral

- HAV and HBV typically
- HDV, HEV, HSV, CMV, EBV, HVZ, paramyxovirus, adenovirus, haemorrhagic fever viruses (HCV rarely causes ALF)

Drugs and toxins (these lists are necessarily incomplete)

- Dose-dependent: acetaminophen, CCl_4, yellow phosphorus, *Amanita phalloides, Bacillus cereus toxin,* sulphonamides, tetracycline, Ecstasy (methyldioxymethamphetamine), herbal remedies
- Idiosyncratic: halothane, INH, rifampicin, valproic acid, NSAIDs, disulphiram

Vascular

- Right heart failure
- Budd–Chiari syndrome
- Veno-occlusive disease
- Shock liver (ischaemic hepatitis)
- Heat stroke

Metabolic

- Acute fatty liver of pregnancy
- Wilson's disease
- Reye's syndrome
- Galactosaemia
- Hereditary fructose intolerance
- Tyrosinaemia

Miscellaneous

- Malignant infiltration (liver metastases, lymphoma)
- Autoimmune hepatitis, sepsis

Indeterminate

- Includes primary graft non-function in liver transplanted patients

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HVZ, herpes varicella zoster virus; CCl4, carbon tetrachloride; INH, isoniazid; NSAIDs, non-steroidal anti-inflammatory drugs.

- Paracetamol levels may have decreased by the time a patient presents with fulminant hepatic failure (FHF), but it is helpful to document this.
- Serum IgM anti-A antibodies diagnose acute hepatitis A.
- Hepatitis B surface antigen may have already been cleared and hepatitis B surface antibody will not yet have appeared, so the hepatitis B IgM core antibody is necessary for diagnosis. It is very useful to store serum at an early stage, as further virological studies might be needed later on. In patients found to be positive for hepatitis B, serum anti-delta should be checked.
- Antihepatitis C virus antibodies should be checked, but are unlikely to be positive this early in the disease. Diagnosis of acute HCV requires PCR for HCV RNA.
- Hepatitis E serology (the virus is prevalent both in the UK and in foreign travellers).
- Pregnancy testing must be performed in women of childbearing potential.
- In patients with risk factors for thrombo-embolism or vasculopathy, assessment of the liver vasculature using ultrasound Doppler and echocardiography can be helpful.
- Ultrasound of the liver will outline liver architecture and show infiltrating lesions.
- In young patients, rare metabolic and autoimmune disease should be considered. The diagnosis of Wilson's disease is difficult as serum caeruloplasmin is unreliable; in this setting an increased serum-free (unbound) copper may be more reliable than any other study results. An autoimmune hepatitis screen should be sent.

Management

Management is supportive (in an intensive care bed with strict monitoring of vital signs and fluid balance), allowing time for the liver to regenerate. This requires careful attention to the complications of liver failure and aggressive treatment of these as they develop. A proton pump inhibitor or H_2 antagonist is given to prevent gastroduodenal bleeding. Enteral nutrition, or in less severe cases oral caloric supplementation, should be given. Patients in whom transplant is appropriate should be sent to a specialist centre for comprehensive assessment. Artificial liver support may be available in some centres.

Hepatic encephalopathy and cerebral oedema

Grade 1–2 encephalopathy

- Sedation should be avoided as this may worsen confusion.
- Should not receive a high protein diet, although there is debate regarding the benefit of low protein diets.
- Phosphate enemas and lactulose should be administered so that the patient has two semi-soft bowel motions per day.

Grade 3–4 encephalopathy

- Patients generally require sedation and mechanical ventilation (risk of concomitant cerebral oedema is high).
- Hyperthermia, hypercapnoea, hypoglycaemia and hyperglycaemia must be avoided.
- Specific therapies for raised ICP include mannitol (mainstay of treatment), barbiturates (used less commonly than previously), hypothermia (experimental), hypertonic normal saline, vasopressors, hepatectomy and liver transplantation.

Renal, metabolic and electrolyte disturbances

- Hypoglycaemia is treated with 100 ml 50% glucose intravenously if the blood sugar falls below 3 mmol/l, followed by an infusion of 5% or 10% dextrose. The blood glucose should be checked at least hourly. Further 50% glucose is given if it falls again.
- Iatrogenic hypokalaemia must be carefully monitored for and replaced.
- Hypocalcaemia, hyponatraemia, hypophosphataemia and hypomagnesaemia are common and require adequate replacement.
- Adequate volume repletion and the avoidance of nephrotoxins are central to the maintenance of renal function. Renal replacement therapy should be undertaken early in established renal failure. Continuous, rather than intermittent, treatment is preferred.

Infection

Regular culture screens should be carried out, including daily sputum and urine culture. Line sites must be carefully monitored. Antibiotics are indicated in patients with any clinical suggestion of infection.

The rationale for the use of prophylactic antibiotics is based on the very high risk of infection in ALF and evidence that systemic inflammatory response is important in the pathogenesis of increased ICP in ALF. Attempts to reduce infection with prophylactic antibiotics are successful but serious resistance problems emerge in up to 10% of patients.

Prophylactic antifungals should be considered early because of diagnostic difficulties and the high mortality associated with systemic fungal sepsis.

Circulatory and respiratory dysfunction

The circulatory disturbance of ALF is characterised by vasodilatation and increased cardiac output. Hypotension may respond to volume repletion but many patients will require vasopressor therapy directed by invasive haemodynamic monitoring. The preferred drug for vasopressor support is noradrenaline.

Adrenal dysfunction contributes to refractory hypotension but supraphysiological doses of corticosteroids, while reducing norepinephrine requirements, do not improve survival.

The main mechanism of lung injury is adult respiratory distress syndrome with or without pulmonary sepsis. Sepsis, haemorrhage, pleural effusions, atelectasis and intrapulmonary shunts can also contribute to respiratory difficulty. Pulmonary sepsis should be aggressively sought and treated.

Coagulopathy

Patients should routinely receive intravenous vitamin K. Because the prothrombin time is an important prognostic variable, infusion of fresh frozen plasma is advocated only for control of bleeding or at the time of invasive procedures. Thrombocytopaenia, with or without disseminated intravascular coagulation, correlates much more closely with the risk of clinical bleeding than INR, and should be monitored closely.

Bioartificial liver support and liver transplantation

A variety of extracorporeal liver-support devices, such as haemodialysis, haemofiltration, charcoal haemoperfusion, plasmapheresis and exchange

transfusions, have been advocated and essentially serve as toxin filters. More recently bio-artificial livers using cell-based therapies have been developed. Despite promising case reports and small series, no controlled study has shown a long-term survival benefit. These techniques seem to be better at 'bridging' patients to transplantation than at improving transplant-free survival.

Liver transplantation (see Chapter 30), although never subjected to a prospective controlled trial, is considered the only proven therapy. Before the era of liver transplantation, less than a half of the patients with ALF survived. Nowadays, liver transplantation for ALF offers an overall survival of 65–80%. However, the outcome remains worse than in those transplanted for chronic liver disease.

Living donor liver transplantation is now established in some centres and is being increasingly used due to the scarcity of deceased donor organs. Auxiliary liver transplantation, where a partial liver graft is transplanted while leaving part of the native liver *in situ*, has been used for patients in whom there is anticipation of recovery of normal liver function. Total hepatectomy with portocaval shunting is a temporising measure that may be employed as a method of stabilising a critical patient until a donor liver becomes available.

10

Pancreatobiliary emergencies: acute pancreatitis

Acute inflammation of the pancreas can arise from a variety of insults, frequently involves peripancreatic tissues and at times remote organ systems. It is potentially lethal and appears to be increasing in incidence. The diagnosis is based on characteristic abdominal pain and nausea, combined with elevated serum levels of pancreatic enzymes. To ensure best management, the diagnosis must be considered early, the disease severity assessed to guide decision-making and adequate fluid resuscitation instituted immediately.

Epidemiology

This is a common emergency condition, with incidence rates up to 80 in 100 000 per year. There has been an apparent increase in the incidence of acute pancreatitis in the past 40 years. This may be due to improved diagnostic capability during this period but may also reflect a true increase due to a greater prevalence of risk factors such as increased alcohol consumption.

The mortality in patients with acute pancreatitis is approximately 5%. About half of deaths occur within the first 2 weeks of illness, generally attributed to organ failure.

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Aetiopathogenesis

In acute pancreatitis the pathological process involves inflammation, oedema and necrosis of pancreatic tissue, as well as inflammation and injury of extrapancreatic organs. Although alcohol abuse and gallstone disease cause 70–80% of acute pancreatitis, a range of other insults can lead to the same end result. The exact mechanisms by which these factors initiate acute pancreatitis are presently unknown. In the case of gallstones or microlithiasis (sludge), it probably involves increased ductal pressure. With prolonged alcohol intake (>100 g/day for >3–5 years), protein plugs may form in small pancreatic ductules. Obstruction by these protein plugs may cause premature activation of pancreatic enzymes. An alcohol binge in such patients can trigger pancreatitis by activating pancreatic enzymes.

Pancreatobiliary anatomy and mechanical causes

Because of the association of the pancreatic duct with the bile duct, obstruction can occur when biliary material impacts in the common segment of the common bile and pancreatic duct (Figure 10.1). This is more likely to occur when biliary sludge and small debris are involved.

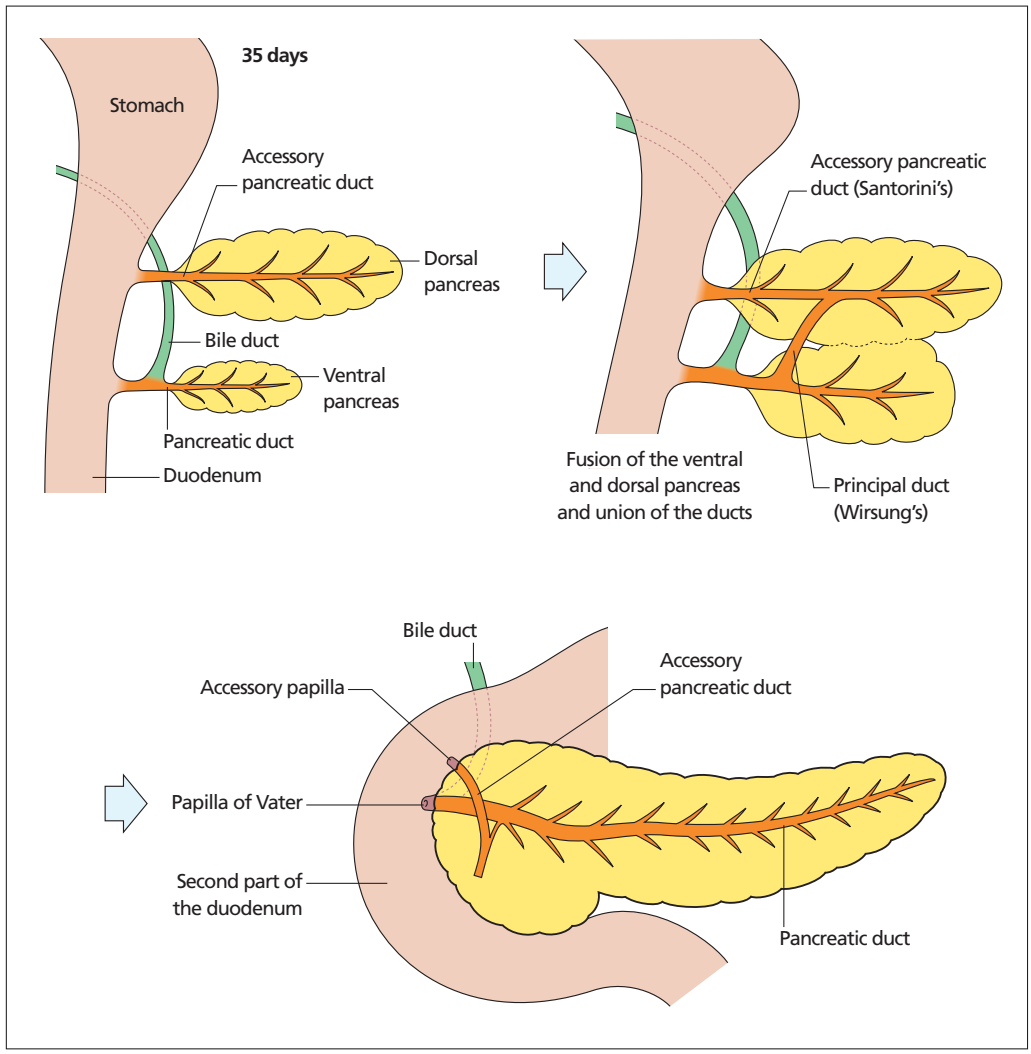

Figure 10.1 Development and normal anatomy of the pancreas.

For similar reasons, dysfunction of the sphincter of Oddi, with very high sphincter pressures, may lead to pancreatitis. One of the complications of endoscopic retrograde cholangiopancreatography (ERCP) is acute pancreatitis, occurring at a rate of up to 15% following complex ERCP. Other types of trauma and pancreatic and periampullary tumours can also precipitate pancreatitis. Finally, a rare cause of pancreatitis may be pancreas divisum where there is failure of the dorsal and ventral ducts to fuse in the embryo so that most of the pancreatic juice flows through the minor pancreatic duct and papilla (Figure 10.1). A comprehensive list of causes is listed in Table 10.1.

Complications

Systemic inflammatory response syndrome

With inflammation of the pancreas comes activation of pancreatic enzymes (including trypsin,

Table 10.1 Causes of acute pancreatitis.

Cause	Example
Drugs	α-methyldopa 5-aminosalicylate ACE inhibitors Azathioprine Cimetidine Cytosine arabinoside Dexamethasone Ethinylestradiol Frusemide Isoniazid Mercaptopurine Metronidazole Norethindrone Pentamadine Procainamide Stilbogluconate Sulphamethazole Sulphamethoxazole Sulindac Tetracycline Trimethoprim
Infectious	Coxsackie B virus, cytomegalovirus, mumps
Inherited	Multiple known gene mutations, including a small percentage of cystic fibro sis patients
Mechanical/ structural	Gallstones, ERCP, trauma, pancreatic or periampullary cancer, choledochal cyst, sphincter of Oddi stenosis, pancreas divisum
Metabolic	Hypertriglyceridaemia, hypercalcaemia (including hyperparathyroidism)
Toxins	Alcohol, methanol
Other	Pregnancy, postrenal transplant, ischaemia from hypotension or atheroembolism, tropical pancreatitis

phospholipase A_2 and elastase) within the gland itself. These enzymes in turn damage tissue, activating complement and the inflammatory cascade, thus producing cytokines. Inflammatory products that enter the systemic circulation produce a systemic inflammatory response. This can result in acute respiratory distress syndrome, cardiovascular failure and renal failure. The systemic effects are mainly mediated through an increase in capillary permeability and decrease in vascular tone.

Other complications

The result of acute pancreatitis is effectively a chemical burn, as activated enzymes and cytokines enter the peritoneal cavity, resulting in capillary leakage of pancreatic fluid.

- **Pseudocysts**: in about 40% of patients, collections of pancreatic fluid and tissue debris form around the pancreas. In half the cases these collections resolve spontaneously; in the remainder either infection sets in or the collections become surrounded by a fibrous (not epithelial)-lined capsule and are called pseudocysts. These pseudocysts may themselves become infected, haemorrhage or rupture.
- **Metabolic complications** of pancreatitis include:
  - Hypocalcaemia (a drop in serum calcium is usually due to concomitant hypoalbuminaemia; however, ionised calcium may fall due to intraperitoneal saponification);
  - Hypomagnesaemia;
  - Hyperglycaemia.
- **Haematological complications** in the form of disseminated intravascular coagulopathy may occur.
- **Infectious complications** may complicate severe pancreatitis, where there is necrosis and haemorrhage of the gland. The necrotic tissue may become infected by enteric bacteria after 5–7 days. In addition, pancreatic pseudocysts may become infected.

History

The main symptom of acute pancreatitis is **abdominal pain** that is usually epigastric in location. It typically increases in severity over a few hours before reaching a plateau that may last for several days. The pain radiates through to the back in about 50% of patients. Sitting up and leaning forward may reduce pain, but coughing, vigorous movement and deep breathing may accentuate it. **Nausea and vomiting** are common. Gallstone pancreatitis may be more sudden in onset whereas that associated with alcoholism may come on more slowly.

Pain beyond about a week is likely to result from the development of local complications.

Examination

Observation reveals an acutely ill and sweaty patient who is tachycardic and tachypnoeic. BP may be transiently high or low, with significant postural hypotension. Temperature may be normal or even subnormal at first but may increase to 37.7–38.3°C within a few hours. Level of consciousness may be reduced. Respiratory examination may reveal basal crackles consistent with atalectasis.

Abdominal signs may vary from mild tenderness to generalised peritonitis. Blue–grey discolouration of the flanks, due to exudation of fluid stained by pancreatic necrosis into the subcutaneous tissue, is known as Grey–Turner's sign. Similar discoloration in the periumbilical area is known as Cullen's sign. In about 20% of patients there will be upper abdominal distension caused by gastric distention or displacement of the stomach by a pancreatic inflammatory mass. Pancreatic duct disruption may cause ascites (pancreatic ascites). Bowel sounds may be hypoactive.

Box 10.1 Ranson's prognostic signs help predict the prognosis of acute pancreatitis.

Five of Ranson's signs can be documented at admission:

- Age > 55 years
- Serum glucose > 11.1 mmol/l (>200 mg/dl)
- Serum LDH > 350 IU/l
- AST > 250 U
- WBC count >16 000/µl

The rest are determined within 48 h of admission:

- Hct decrease >10%
- BUN increase > 1.78 mmol/l (>5 mg/dl)
- Serum Ca < 2 mmol/l (>8 mg/dl)
- PaO_2 < 60 mmHg (<7.98 kPa)
- Base deficit > 4 mmol/l (>4 mEq/l))
- Estimated fluid sequestration > 6 l

Mortality increases with the number of positive signs:

- <3 signs are positive, the mortality rate is <5%
- 3–4 signs positive, the mortality rate is 15–20%

Risk stratification

In assessing the patient with acute pancreatitis, stratification of the severity of an episode is essential as it guides appropriate allocation of critical care beds, ERCP, CT scanning and nutritional support. The severity of acute pancreatitis is defined by the presence or absence of organ failure, local complications, or both, and can be assessed using specific scoring systems. The best known of these is the Ranson criteria, completed 48 h after onset of the episode (Box 10.1).

Elevated C-reactive protein levels at 24–48 h after onset are also useful in predicting severity. In addition there are markers of severity not included in standard scoring systems that should be considered:

- Obesity (a BMI of >30) is associated with a 2–3 fold increase in the risk of a severe clinical course;
- A haematocrit > 44% is a clear risk factor for pancreatic necrosis, although it is a poor predictor of the severity of disease;
- Several clinical findings, including thirst, poor urine output, progressive tachycardia, tachypnoea, hypoxaemia, agitation, confusion, a rising haematocrit level and a lack of improvement in symptoms within the first 48 h are warning signs of impending severe disease.

Investigations

The diagnosis of acute pancreatitis is made in the presence of typical **clinical features** together with a high plasma concentration of **pancreatic enzymes**. Serum amylase analysis is the most widely available test. However, concentrations decline quickly over 2–3 days. In addition, hyperamylasaemia is found in several non-pancreatic diseases and its specificity for acute pancreatitis is around 88%. Diagnosis should therefore not rely on arbitrary limits of values three or four times greater than normal. Lipase

has a superior sensitivity and specificity for acute pancreatitis.

Following a thorough history and physical examination, all patients should have:

- Serum amylase (and if available lipase);
- FBC;
- Electrolytes and renal function;
- Coagulation screening;
- Liver enzymes;
- Serum lactate;
- Calcium, magnesium;
- Glucose;
- Arterial blood gases and pH;
- Biliary ultrasonography.

Any abnormalities should be monitored and tests repeated within 48 h to allow further risk stratification.

Follow-up investigations, during the recovery phase, should include fasting plasma lipids and calcium, as both may be secondarily reduced during the acute episode. Convalescent viral antibody titres and repeat biliary ultrasonography are warranted if the cause is not obvious. Further investigations are indicated by the clinical situation.

For **recurrent idiopathic acute pancreatitis**, exclusion of the following is essential:

- Pancreatic cancer;
- Microlithiasis;
- Chronic pancreatitis;
- Pancreas divisum.

This is undertaken by:

- Ultrasonography: considered the investigation of first choice because of its ability to show gallstones and dilated bile ducts. Its weakness is in detecting stones within the lower and common bile duct;
- CT: mainly indicated for the detection and staging of the complications of acute severe pancreatitis, especially pancreatic necrosis;
- Endoscopic ultrasonography: perhaps the most sensitive modality for detecting biliary causes and may guide the use of ERCP;
- ERCP: may be needed to detect microlithiasis or provide sphincter of Oddi manometry; its main role in acute pancreatitis currently is the treatment of biliary causes;
- MRI: like CT, can identify gallstones or a tumour, as well as local complications. MRI may also identify early duct disruption that is not seen on CT.

Management

- Aggressive fluid resuscitation is the central aspect of management of acute pancreatitis.
- Treatment of pain usually requires opiate analgesia and, while morphine is generally avoided because of concerns that it might exacerbate pancreatitis by increasing sphincter of Oddi tone, no definitive human study supports this.
- Early risk stratification guides allocation to critical care and nutritional support.

Nutritional support

Early enteral nutrition should be the goal for all patients with acute pancreatitis. Nutritional support is essential for all patients with severe disease. Enteral nutrition is superior to parenteral in terms of cost, safety and risk of septic complications. In severe pancreatitis, the nasojejunal route of feeding is usually recommended. However, a clear benefit of this over nasogastric feeding has not been shown. Serum glucose concentrations should be monitored and in the critically ill patient should be maintained at or below 6.1 mmol/l by the use of intensive insulin treatment.

Gallstones

ERCP and sphincterotomy within 72 h of disease onset is indicated for patients with acute severe gallstone pancreatitis. In patients with mild gallstone pancreatitis, it is important to prevent recurrence. A cholecystectomy with intraoperative cholangiography should be undertaken as soon after recovery as possible; if the patient is not fit for cholecystectomy, then ERCP and sphincterotomy is sufficient.

Other treatment modalities

Antibiotic prophylaxis is effective in preventing infection of necrotic pancreatic tissue. However, it is also associated with the development of antibiotic resistance and is reserved for patients with pancreatic necrosis proven on CT. Antibiotics

should be used early when infection is suspected. Initial therapy is with agents active against enteric organisms.

If patients have >30% necrosis on CT scanning, then further investigation to detect infected necrotic tissue is indicated. Positive bacteriology from samples gained by fine needle aspiration of pancreatic or peripancreatic necrotic tissue, or the presence of retroperitoneal gas on CT, is an indication for necrostomy. The standard techniques for necrostomy are surgical, however radiological and endoscopic techniques have been trialled.

11

Oral cavity

The oral cavity is the first portion of the digestive system: it receives food, commences digestion by mechanically breaking up the solid food into smaller particles and then combines these with saliva.

Oral ulcers

Aphthous ulcers are the commonest causes of oral ulceration. These are painful, superficial breaches of the mucosa of the lips, tongue, gums or buccal membranes. They are recurrent in up to a third of the normal population, but if other systemic features are present, then alternative causes need to be considered (Box 11.1).

Usually just antiseptic mouthwashes will suffice to allow spontaneous healing, but topical salicylates or steroids can induce rapid healing. Rare patients with severe, recurrent ulcers need oral steroids.

Oral cancer

Squamous cell carcinoma is increasing in incidence, and is aetiologically related to:

- Smoking or tobacco chewing;
- Alcohol excess;
- Malnutrition;
- Betel nut chewing (in Asian populations).

It may present as a lump, or an ulcerated lesion or a white patch in the mouth ('leukoplakia'). Cervical lymphadenopathy is usually a sign of late presentation. Radical radiotherapy is often undertaken, and is preferable to surgical resection, which often needs extensive dissection.

Oral manifestations of inflammatory bowel disease

Crohn's disease

- 0.5% of Crohn's patients show oral features.
- Usually young males, often co-existing with anal Crohn's.
- Usually multifocal, firm painless lumps (unless ulcerated, see Box 11.1).
- Diagnosis confirmed by biopsy.
- Usually self-limiting, may need topical steroid.

Ulcerative colitis

- Rarer than oral Crohn's.
- Usually male, any age.
- Usually multifocal, shallow, pustular lesions.
- Usually responds to treatment of colonic disease.
- Occasionally needs topical steroid or dapsone.

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Box 11.1 Causes of oral ulceration

Idiopathic aphthous ulcers

GI disease
- Coeliac disease
- Crohn's disease

Infection
- Herpes simplex
- Vincent's angina
- Candidiasis

Systemic disease
- SLE
- Behcet's disease
- Pemphigus
- Pemphigoid

Drugs
- Stevens–Johnson syndrome

Neoplasia
- Oral cancers
- Leukaemia

Dental enamel erosion

Can arise from GI causes:

- Gastro-oesophageal reflux disease;
- Chronic alcoholism (recurrent vomiting, neglect and malnutrition);
- Recurrent vomiting in bulimia.

Hereditary haemorrhagic telangiectasia

Four forms of this autosomal dominant disorder are described. All are characterised by:

- Mucosal and skin telangiectasia;
- Arteriovenous malformations (AVMs) in the internal organs.

Gardner syndrome

An autosomal dominant (chromosome 5) disorder of intestinal polyposis (with high rates of developing into cancer). Head and neck features are prominent:

- Unerupted teeth;
- Jaw osteomas;
- Jaw enostoses (growths on internal surface of bone cortex);
- Epidermoid cysts on head and neck.

Peutz-Jegher's syndrome

An autosomal dominant (chromosome 19) disorder of benign hamartomatous intestinal polyps and hyperpigmented macules on the lips and oral mucosa. Patients are at increased risk of all cancers, particularly GI and pancreatic, so once diagnosed, screening is mandatory.

12

Oesophagus

Gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux (GOR) is one of the most prevalent symptoms, with 10–20% of the population in the developed world experiencing at least weekly heartburn. Given the high prevalence of GOR symptoms, it should only be considered a disease when frequent symptoms or complications occur.

Aetiology

In health, GOR episodes occur throughout the day, especially after meals. However, these do not usually cause symptoms due to the following antireflux mechanisms:

- Lower oesophageal sphincter (LOS) pressure: the tone produced by the combination of smooth circular muscle at the distal oesophagus and striated muscle of adjacent diaphragm. The LOS resists the pressure gradient from abdomen to thorax that predisposes towards reflux. The LOS normally relaxes to allow food into the stomach, and also does so several times a day to allow swallowed air out of the stomach – these are called *transient LOS relaxations (TLOSRs)*.
- Angle of Hiss: the oblique angle between the cardia and oesophagus, which provides an anatomical barrier (Figure 12.1a).
- Oesophageal clearance: any material refluxed into the oesophagus is normally rapidly cleared back into the stomach by oesophageal contractions.

Impairment of any of these defences may result in reflux symptoms.

- **Hiatus hernia** herniation of the stomach into the thorax. Although present in 30% of over 50 year olds, it is usually asymptomatic. There are two forms: sliding (much commoner) and rolling (Figure 12.1b). A hiatus hernia causes reflux by reducing LOS pressure, increasing TLOSRs and straightening out the angle of Hiss. A very rare complication of a hiatus hernia is development of **gastric volvulus** when the stomach twists on itself causing severe pain and dysphagia; diagnosis is by chest X-ray showing a thoracic air bubble, and management is by nasogastric tube decompression followed by surgical referral
- **Gastroparesis** – any condition that delays gastric emptying (pregnancy, binge drinking, poorly controlled diabetes) can increase gastric volume and hence the pressure gradient encouraging reflux. TLOSRs are also prolonged in gastroparesis. This is why eating large, calorie-rich meals (especially before lying flat) promotes reflux.
- **Increased intra-abdominal pressure**: pregnancy, obesity and chronic cough all increase the pro-reflux pressure gradient – hence weight loss may help GOR symptoms.
- **Unhealthy lifestyle** smoking, eating fat- and calorie-rich foods and binge drinking reduce LOS pressure and increase TLOSRs. These factors, and regular use of NSAIDs, also increase gastric acid production, resulting in more acid being available to cause reflux.

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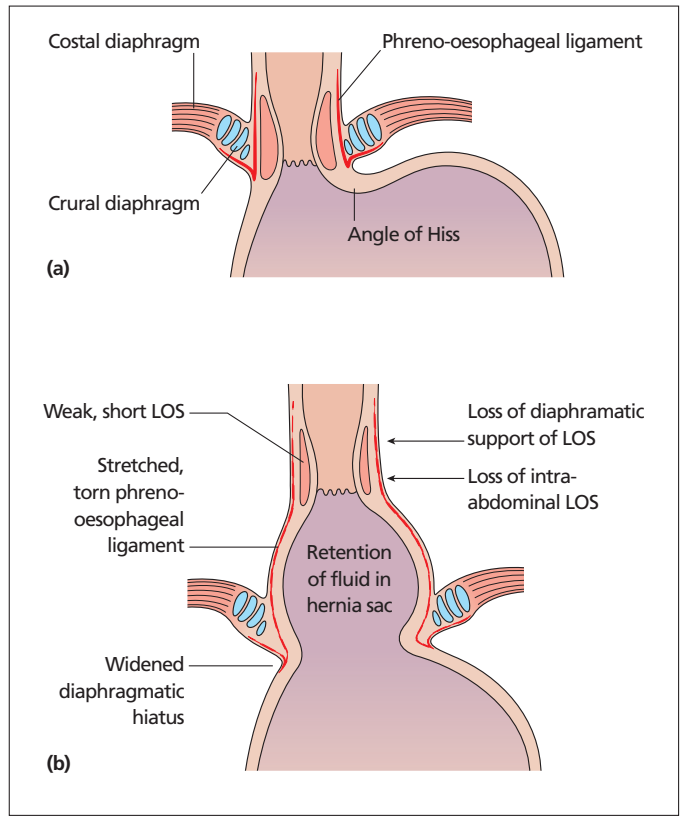

Figure 12.1 (a) Normal distal oesophagus and proximal stomach; (b) Distal oesophagus and proximal stomach with hiatus hernia (LOS = lower oesophageal sphincter).

Clinical features

- Heartburn } related to bending,
- Fluid/food regurgitation } straining and tight clothing;
- Waterbrash (= reflex salivation in response to oesophageal acid);
- Nocturnal cough (due to gastric fluid refluxing to the larynx when lying flat);
- Chest pain (secondary to acid-related oesophageal muscle spasm);
- Dysphagia or odynophagia (= painful or difficult swallowing) are rare in uncomplicated GORD

Investigations

Indicated in middle-aged or elderly patients with alarm symptoms present. Endoscopy is the first-line investigation (to exclude other conditions causing similar symptoms). 24-h pH measurement is helpful if surgery is being considered or the exact diagnosis is unknown. *Note*: there is poor correlation between endoscopic change, degree of acid reflux (on pH testing) and burden of symptoms.

Clinicopathological manifestations

- **Oesophagitis**: defined as endoscopic change ranging from minor erythema to frank ulceration and stricturing (classified as Los Angeles grades A to D, respectively). Anaemia from oesophagitis is rare and if present, another cause of anaemia should be sought.
- **Oesophageal stricture** (Box 12.1): this typically complicates severe and chronic oesophagitis and results in narrowing of the distal oesophagus following repeated peptic ulceration and scarring. It presents as dysphagia and requires treatment by

Box 12.1 Causes of oesophageal stricture (seen at endoscopy or barium swallow).

- Peptic ulceration secondary to GORD (*majority*)
- Achalasia
- Schatzki ring (distal oesophageal fibrotic rings)
- Post-cricoid web (usually distal) – termed Patterson–Kelly or Plummer–Vinson syndrome when present with iron-deficiency anaemia
- Carcinoma of the oesophagus (or gastric cardia)
- Postoperative or post-radiotherapy
- Following corrosive ingestion
- Eosinophilic oesophagitis (young patient)
- Viral oesophagitis (immunocompromised patient)
- Extrinsic compression (lung cancer, enlarged lymph nodes, aortic aneurysm)

endoscopic dilatation. At this time, biopsies may help to exclude malignancy. Following dilatation, long-term PPIs are indicated (both as secondary prevention and to minimise reflux symptoms after dilatation).

- **Barrett's oesophagus**:
  - Also known as columnar-lined oesophagus, this is an endoscopic or pathological diagnosis defined as metaplasia of distal oesophageal mucosa from squamous to columnar epithelium. It is thought to arise as an adaptive response to chronic acid exposure;
  - Typically asymptomatic;
  - Its importance lies in the fact that it is a premalignant condition, with a lifetime risk of 10% of developing oesophageal adenocarcinoma. This is a cancer that is rapidly increasing in incidence. However, it is important to remember that the actual rate of developing cancer is low, incidence figures being 1 in 200 patient years. Particularly at risk are:
    - White males;
    - Over 50 year olds;
    - The obese;
    - Smokers (though not alcohol misusers).
  - Diagnosis is based on mucosal appearances and histology; multiple biopsies should be taken to look for **intestinal metaplasia** (a histological precursor of malignancy);
  - There are a range of management options:
    - Acid suppressive therapy does not induce regression of Barrett's oesophagus;
    - Endoscopic ablation through photodynamic therapy is effective, but is associated with significant local side-effects (nausea, dysphagia, chest pain) and may result in 'buried islands' of Barrett's mucosa under the epithelium;
    - Antireflux surgery does not stop progression of Barrett's oesophagus;
  - Surveillance frequency depends on the severity of dysplasia but the value of this surveillance remains controversial;
  - When high-grade dysplasia is observed, oesophagectomy may be considered in patients fit enough for such surgery since 40% will be found to have a cancer present at resection.

Management

Conservative

- **Lifestyle modification** strategies (weight loss, smoking cessation, avoiding fatty meals prior to bedtime, elevation of the bed head) are usually complied with poorly.
- **Antacids** provide effective symptom relief for 40% of patients and may be needed several times a day.

Medical

- **H_2 receptor antagonists** are as effective as antacids and need be taken less frequently.
- **Proton pump inhibitors (PPIs)** achieve symptom relief in the overwhelming majority of patients, and are especially effective when symptoms are severe. Unlike other medical agents, they also heal oesophagitic mucosa. The newer PPIs are licensed for 'on demand' use to relieve symptoms. Some patients need long-term treatment, in which case the lowest effective dose should be used. According to patient preference – and for the rare patient who does not respond to PPIs – consideration of more interventional treatments (see below) may be needed.

Endoscopic

- **Endoscopic fundoplication** is an experimental technique for patients with significant symptoms in the context of a small or no hiatus hernia.

Surgical

- **Laparoscopic or open fundoplication** is the more established – and more invasive – method to treat refractory reflux symptoms. It is suitable for patients with large hiatus hernias. However, it is not curative (>60% of patients need to restart PPIs) and it does not prevent Barrett's cancers. It may be more cost-effective than maintenance PPI use, but only after 8 years. Adverse effects are seen in up to 15% of patients:
  - Dysphagia;
  - Excess flatulence;
  - 'Gas-bloat' syndrome (inability to belch).

Caustic oesophagitis

Corrosive ingestion

Deliberate self-harm through ingestion of bleach or battery acid causes acute oropharyngeal and oesophageal ulceration, and stricture formation in the chronic situation. Management is with analgesia, antiemetics and keeping the patient nil by mouth. Acutely, oesophageal perforation is the major risk, and endoscopy should be avoided. If dysphagia develops later on, endoscopic dilatation of any strictures may be performed, but is hazardous.

Drug-induced oesophagitis

NSAIDs, potassium supplements and bisphosphonates may cause oesophageal ulceration, especially if the tablets get stuck above an oesophageal stricture. Liquid or parenteral preparations should be considered in patients with known strictures.

Oesophageal motility disorders

Achalasia

This is a not uncommon oesophageal motility disorder that can occur at any age, but most typically middle age.

Achalasia is characterised by:

- Failure of propagation of peristalsis in the body of the oesophagus;
- Progressive dilatation of the body of the oesophagus;
- Failure of relaxation of the LOS;
- High pressure LOS.

The cause is degeneration of the ganglia in the distal oesophagus and LOS (related to disturbed nitric oxide synthesis). Destruction of the myenteric plexus, causing a similar clinical syndrome is seen with oesophageal cancer and Chagas disease.

Clinical features

- Dysphagia:
  - Insidious, initially intermittent;
  - For solids, eased by liquids;
  - Worse if swallowing whilst slouched.
- Heartburn (may occur despite increased LOS pressure).
- Chest pain.
- Regurgitation } in late stages
- Pulmonary aspiration } of the disease.

A rare complication is squamous carcinoma of the oesophagus.

Investigations

- Oesophageal manometry is diagnostic (Figure 12.2):
  - Absent peristalsis (always);
  - Poor LOS relaxation (frequent);
  - High LOS pressure (occasional).
- Barium swallow (tapered narrowing of distal oesophagus with proximal dilatation and aperistalsis).
- Upper GI endoscopy is mandatory (to exclude carcinoma '*pseudo-achalasia*').

Management

Medical

- Drugs which reduce LOS pressure (calcium channel antagonists, nitrates) are not usually clinically helpful.

Endoscopic

- Forced pneumatic dilatation: this benefits 80% of patients, but may need to be repeated. The perforation rate for each procedure is 1–2%.

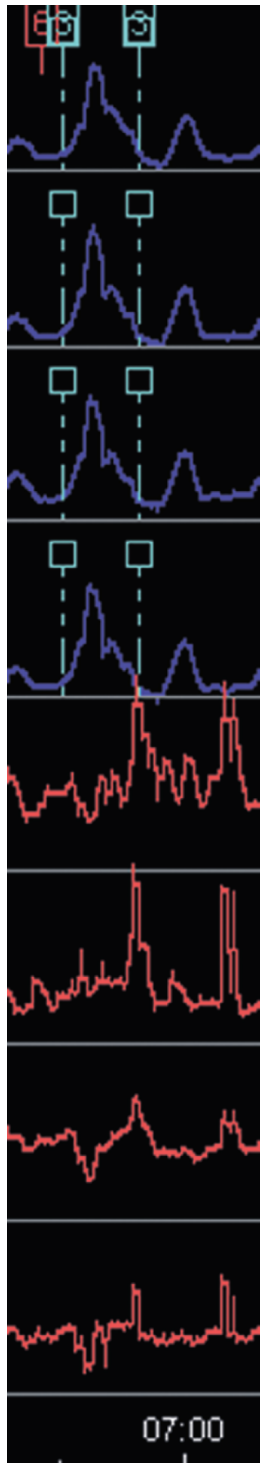

Figure 12.2 Stationary oesophageal manometry study showing simultaneous contractions in upper four traces and non-relaxing high pressure LOS in lower four traces.

- LOS botulinum toxin injection: benefits as many, but short-lived efficacy. Both procedures are complicated by the development of GORD, and so co-prescription of a PPI is needed.

Surgical

- Heller's myotomy (performed 'open' or laparoscopically) is indicated in young patients or those requiring multiple dilatations. As with endoscopic procedures, reflux is common, so fundoplication is also often undertaken.

Diffuse oesophageal spasm

This typically presents with angina-like chest pain (with or without dysphagia) in middle age. The pain is thought to be triggered by smooth muscle spasm in response to reflux. Oesophageal manometry (see Chapter 6) and 24-h pH are required for diagnosis. Treatment therefore depends on the use of a PPI. Nitrates and calcium channel antagonists may also relieve pain. Endoscopic dilatation and surgical myotomy are not often effective.

'Nutcracker' oesophagus

Extremely high amplitude contractions can cause chest pain and dysphagia. Diagnosis is by manometry. Treatment is with nitrates and calcium channel antagonists.

Non-specific motility disorders

A variety of manometric abnormalities are observed in one-third of patients (especially the elderly) with chest pain and dysphagia. These abnormalities (e.g. ineffective peristalsis, high pressure LOS, low pressure LOS) do not necessarily relate to symptoms, and no specific treatment is indicated.

Systemic sclerosis (and to a lesser extent other connective tissue disorders) can involve the oesophagus, resulting in failure of peristalsis, and hence dysphagia and heartburn. Long-term treatment is with PPIs to prevent peptic strictures.

Oesophageal tumours

Gastrointestinal stromal tumours (GISTs)

These are rare benign lesions that are usually asymptomatic and observed at endoscopy

performed for another reason. No treatment is required as long as they do not cause symptoms.

Oesophageal carcinoma

- **Adenocarcinoma**: typically lower third of the oesophagus (see Barrett's oesophagus above). Its incidence is increasing (5 in 100 000 in the UK).
- **Squamous carcinoma**: can occur anywhere along oesophagus. Less common than adenocarcinoma in the Western world; very common in Iran and Far East. *Risk factors*: smoking, alcohol, betel nut and tobacco chewing, achalasia, post-cricoid web, coeliac and post corrosive ingestion.
- **Small cell cancer**: very rare.

Clinical features

- Painless, rapidly progressive dysphagia is classical.
- Weight loss.
- Chest pain (usually late, suggests local invasion).
- Hoarse voice (usually late, suggests local invasion).
- Coughing after swallowing, pneumonia or pleural effusion suggests oesophagobronchial fistula.
- *Acutely*: bolus obstruction.
- Examination may be normal until late – look for cervical nodes.

Investigations

- Upper GI endoscopy: demonstrates site and allows histological sampling.
- Barium swallow: demonstrates length of stricture if the tumour could not be intubated at endoscopy.
- CT of the thorax and abdomen: for staging.
- Endoscopic ultrasound: best staging modality.

Management

- 30% have 'operable' disease (not spread beyond the oesophagus):
  - Oesophagectomy;
  - Preoperative chemotherapy.
- 70% have inoperable disease at presentation:
  - Palliation of dysphagia by endoscopic stenting or laser;
  - Palliation of pain with potent analgesia;
  - Squamous cancers (and to a lesser extent adenocarcinomas) may be palliated by radiotherapy;
  - Provision of nutritional supplementation.

Prognosis

Overall 5-year survival is <10%. If the tumour is operable, 5-year survival is 30%.

Oesophageal endoscopic abnormalities

Pharyngeal pouch

See Box 12.2. Also known as Zenker's diverticulum. The major importance of this condition is that it is a potential cause of perforation at endoscopy; if suspected, the first-line investigation is a barium swallow. pouch

Eosinophilic oesophagitis

Eosinophilic oesophagitis is a recently described condition characterised by eosinophilic infiltration of the mucosal layer of the oesophagus. It can be due to an allergic trigger and may occur in isolation or as part of a generalized eosinophilic gastroenteritis.

- Males are affected twice as often as females.
- Two age peaks at diagnosis: in children and in the early 30s.
- Paediatric cases typically present with vomiting, and adults with dysphagia.
- Diagnosis is based on the presence of >20 eosinophils/high power field (hpf), since reflux oesophagitis is associated with up to 10 eosinophils/hpf.

Box 12.2 Features of pharyngeal pouches.

- Patient: elderly, especially males
- Symptoms: dysphagia, night-time cough, halitosis, lump in throat or gurgling after eating
- Cause: inco-ordinate swallowing, results in herniation through cricopharyngeus
- Diagnosis: barium swallow
- Treatment: surgery (myotomy and pouch resection

- Treatment with elemental or elimination diets is beneficial in children.
- Steroid therapy is indicated in diet-refractory patients, with systemic steroids more effective than topical.
- Rarely, patients presenting with oesophageal strictures may need endoscopic dilatation.

Oesophageal rings and webs

These are typically seen at radiology rather than at endoscopy. Schatzki's ring is a circumferential narrowing in the mid or lower third of the oesophagus, whilst oesophageal webs are not circumferential and proximal. If iron-deficiency anaemia is associated with an oesophageal web, the condition is known as Plummer–Vinson syndrome. They are usually asymptomatic. They may cause intermittent dysphagia to solids over many years, in which case dilatation is required.

Mallory-Weiss tear

This is a cause of **haematemesis** (see Chapter 7). It is caused by recurrent retching or forceful vomiting (typically after alcohol binges), resulting in a mucosal tear of the oesophogastric junction. The characteristic history is that the initial vomitus does not contain blood. Most cases settle spontaneously. Acid suppression medication and endoscopic therapy are only rarely necessary.

13

Stomach and duodenum

Gastritis

Strictly speaking, this is a histological diagnosis, and there is poor correlation with endoscopic appearances. Classification is according to:

- Type (acute, chronic, special form);
- Site (antrum, body, whole stomach);
- Morphology (inflammation, atrophy, metaplasia, *Helicobacter pylori*);
- Aetiology (*H. pylori*, autoimmune, alcohol, NSAID, post gastrectomy).

Features are summarised in Table 13.1.

Menetrier's disease

This is a rare condition presenting classically with weight loss and diarrhoea (due to protein-losing enteropathy). It is aetiologically linked to *H. pylori*, leading to achlorhydria. Endoscopically there is hypertrophy of mucosal folds of the body and fundus. Histologically, mucus-secreting cells replace parietal cells. Treatment is to eradicate *H. pylori*, reduce secretion (with proton pump inhibitors [PPIs]) and monitor endoscopically due to risk of gastric cancer.

Peptic ulcer disease

Peptic ulcers are caused by an imbalance between luminal acid and mucosal defences. Hydrochloric acid (pH 1) and pepsin are secreted from the gastric pits, but do not damage the mucosa in health because of a layer of overlying unstirred mucus. This mucus layer has bicarbonate secreted into it, maintaining a pH of 7. Prostaglandin and a good capillary blood flow are essential for this mucus and bicarbonate secretion, explaining how NSAIDs and smoking may predispose to ulcers. Peptic ulcers are becoming less frequent in the developed world due to widespread *H. pylori* eradication.

Peptic ulcers may occur in the distal oesophagus, stomach, duodenum, near a Meckel's diverticulum or any small bowel anastomosis. Pathologically, they are distinct from erosions in that they penetrate the muscularis mucosae. They may be acute or chronic (the latter bearing the pathological hallmark of submucosal fibrosis).

Gastric and duodenal ulcer

The differences between duodenal and gastric ulcers are summarised in Table 13.2.

Gastric ulcer

These are usually benign, but gastric adenocarcinoma may present as an ulcer.

Causes

- *H. pylori*.NSAID use (especially if also *H. pylori* positive).
- Steroid *and* NSAID use.
- Stress (which more often causes gastric erosions than ulcers).

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Table 13.1 Features of gastritides.

	Acute gastritis	Chronic gastritis		Special forms
Aetiology	NSAIDs Alcohol Other drugs Stress (burns, ITU patients) Bile reflux (post-gastrectomy) *H. pylori* Infections (CMV or HSV)	• *H. pylori* (commonest by far) • Autoimmune		Infections (CMV, TB) Crohn's disease Systemic disease (sarcoid, GVHD) Granulomatous gastritis
Presentation		***H. pylori***	**Autoimmune**	
	Asymptomatic usually Rarely dyspepsia, anorexia, retching, haematemesis	Asymptomatic usually	Asymptomatic usually	Asymptomatic usually
Site	Anywhere in stomach	Antral usually	Body usually	Anywhere – can be focal or whole stomach
Histology	Neutrophil infiltrate	Lymphocyte and plasma cell infiltrate	Diffuse inflammation, atrophy, intestinal metaplasia	Depends on cause
Other features	–	Antral predisposes to duodenal ulcer, body predisposes to gastric ulcer (*H. pylori*) May cause mucosal erosions ('erosive gastritis')	Circulating antibodies to parietal cells With severe atrophy there is achlorhydria and loss of intrinsic factor leading to pernicious anaemia	–
Cancer risk	–	Increased risk	Increased risk	–
Treatment	Treat cause Antacids Acid suppression Antiemetics	*H. pylori* eradication	Correct anaemia Look for other autoimmune disease	Treat cause

Clinical features

- Simple ulcers present as described in Table 13.2.
- Complications such as haematemesis or perforation are commoner in the elderly.

Management

- Eradication of *H. pylori* (or 50% will recur) and 4 weeks of PPI (preferred to H_2 receptor antagonists).
- Smoking cessation and alcohol moderation advice.
- Stop NSAIDs if possible.
- Maintenance PPI is indicated if there is major comorbidity or presentation with bleeding.
- Consider surgery (Bilroth partial gastrectomy) if there is:
  - Haemorrhage (seen in 25%);
  - Perforation (in 10%);
  - Failure to heal;
  - Gastric outlet obstruction (with prepyloric ulcers).

Duodenal ulcer

Causes

- *H. pylori* (infection of the antrum depletes somatostatin production, which results in hypergastrinaemia and hence increased acid

Table 13.2 Features differentiating gastric and duodenal peptic ulcers.

	Gastric	Duodenal
Pathophysiology Acid secretion	Normal	Increased
Epidemiology Age Male:female	Elderly especially 2:1	Under 40 year olds especially 4:1
Clinical Epigastric pain Vomiting Other symptoms	Soon after eating, relieved by antacids Not uncommon Loss of appetite and weight common	Nocturnal and hunger pain Rare, only with proximal cap ulcers No loss of appetite or weight
Endoscopy Necessity Biopsy	Diagnosis *and* repeat to check healing at 8–12 weeks Edge of ulcer to exclude malignancy	Diagnosis only Antral biopsy for *H. pylori*
Treatment Simple ulcer Ulcer presenting with GI bleed	*H. pylori* eradication if infection present. Add 4 weeks PPI Get surgical opinion	*H. pylori* eradication only Add 4 weeks PPI

secretion, which in turn results in gastric metaplasia of the duodenum and ulceration).
- NSAID use (especially if also *H. pylori* positive).
- Smoking.
- Stress (especially with chronic illness – renal failure, cirrhosis).

Clinical features

- Simple ulcers present as described in Table 13.2.
- Perforation as a complication is commoner than with gastric ulcer.

Management

- Eradication of *H. pylori* – routine use of PPI is only indicated if there is haemorrhage or recurrence of ulcer symptoms after eradication.
- Smoking cessation and alcohol moderation advice. Stop ulcerogenic drugs (NSAIDs, bisphosphonates) if possible.

Complications

Perforation

- Especially with acute ulcers and NSAID-associated ulcers.
- Acute presentation (see Chapter 1) with severe upper abdominal pain, rapidly becoming generalised.
- Rigid, silent abdomen.
- Free air under diaphragm on upright chest X-ray; if not seen, water-soluble contrast examination will show abnormality.
- Resuscitation and surgery (over-sew of defect or resection).
- 25% mortality.

Gastric outlet obstruction

- May occur with pyloric gastric ulcers, or proximal cap duodenal ulcers.
- May also be caused by gastric antral carcinoma, adult hypertrophic pyloric stenosis.
- Vomiting of 'old' food, abdominal distension.
- Succussion splash, visible gastric peristalsis and dehydration.
- Hypokalaemic alkalosis (due to luminal loss of K^+ and acid).
- Endoscopic diagnosis after stomach content has been aspirated by a nasogastric tube.
- Initial management is '*drip and suck*' – intravenous rehydration and nasogastric aspiration.
- Later management is with balloon dilatation (if possible) or surgical resection/ gastroenterostomy.

Zollinger-Ellison syndrome

Rare disorder with the triad of:

- Severe (i.e. multiple or complicated) or recurrent peptic ulceration (may be throughout upper gut);
- Increased gastric acid secretion;
- Hypergastrinaemia due to secretion from a non-beta cell islet pancreatic tumour.

Diarrhoea and steatorrhoea often occur (due to acid destruction of lipase). 60% of tumours are malignant (albeit slow growing), 50% are multiple and 25% have other endocrine tumours (part of a multiple endocrine neoplasia type I).

Investigations

- **Condition**:
  - Gastric acid secretion: grossly elevated at baseline with little increment following intravenous pentagastrin;
  - Serum gastrin: grossly elevated.
- **Cause**: locate tumour by endoscopic ultrasound or Octreoscan (radiolabelled somatostatin receptor scan).

Management

- 30% resectable (small, single, localisable).
- Lifelong PPI in high doses.
- Octreotide (a somatostatin analogue) may help.

Gastroparesis

This refers to delayed gastric emptying without mechanical obstruction. It may occur as a primary (idiopathic) condition, but may be secondary to autonomic neuropathy (especially secondary to diabetes) or gastroduodenal myopathy (systemic sclerosis, amyloidosis). Early satiety, recurrent vomiting, abdominal bloating and distension are characteristic. Peripherally-acting antiemetics (metoclopramide, domperidone) may help, as may erythromycin (as a motilin analogue). If malnutrition develops, jejunostomy feeding or parenteral nutrition is indicated. Rarely, surgical enterostomy may be needed.

Gastric carcinoma

This is the commonest cause of cancer death worldwide (especially in China and Japan), but is falling in incidence in the UK. It occurs more often in men and those over 50 years old.

Causes

- Chronic *H. pylori* infection (especially the cagA strain) is probably responsible for two-thirds of cases.
- Familial: blood group A is associated, and there are rare gastric cancer families.
- Genetic (rare polyposis syndromes – familial adenomatous polyposis, Peutz–Jegher's syndrome).
- Diet containing *N*-nitrosamines (pickled or smoked foods), diets low in fruit and vegetables.
- Environmental factors such as smoking and alcohol.
- Rarely, organic disorders: Menetrier's disease, previous partial gastrectomy.

Pathology

Adenocarcinoma develops from regions of intestinal metaplasia in the stomach, which themselves develop secondary to chronic atrophic gastritis. The spectrum of pathology ranges from polypoid lesions to diffuse infiltration (*linitis plastica*). The term *early gastric cancer* refers to adenocarcinoma confined to the mucosa or submucosa. It is diagnosed, and can often be cured, endoscopically.

Clinical features

- Epigastric pain (non-specific, unrelated to meals and relieved by acid suppressants), loss of appetite and weight are common.
- Haematemesis is rare and physical signs are rare except in late disease.
- A supraclavicular lymph node (*Troisier's sign*) and migratory thrombophlebitis (*Trousseau's sign*) are rare but classical signs.

Investigations

- **Condition**: endoscopy – rolled irregular-edged ulcers (biopsy the edges)
- **Complications** = staging: FBC and LFTs, chest X-ray, abdominal CT and endoscopic ultrasound; laparoscopy is often required

Management

- **Surgery**: resection is only possible in a minority of cases, and most surgery is palliative.
- **Chemotherapy**: postoperatively this may improve survival, and can also be used palliatively.

Prognosis

Whilst the prognosis for early gastric cancer is good (90% 5-year survival), overall the outlook is dismal (10% 5-year survival). Prognosis would be improved by improved public awareness and early diagnosis.

Gastric lymphoma

The stomach is the commonest site for non-nodal non-Hodgkin's lymphoma.

Primary gastric lymphoma

This affects mostly males over 50 and relative risk is increased in patients with AIDS. These are B-cell tumours, most of which are aggressive large-cell lymphomas, with a minority being low-grade mucosal associated lymphoid tissue tumours ('MALT lymphomas'). Clinical and endoscopic features are similar to gastric adenocarcinoma. Diagnosis rests on histology, from deep mucosal biopsies or laparoscopy. Endoscopic ultrasound and abdominal CT help with staging. Early disease is managed surgically, later disease by chemoradiotherapy.

MALT lymphoma

This is a B-cell tumour caused by an immune response to chronic *H. pylori* infection with cagA strains. These are histologically distinct, with lympho-epithelial lesions and reactive lymphoid follicles. *H. pylori* eradication leads to remission in 75%. Endoscopic mucosal resection, chemoradiotherapy and resectional surgery are only rarely needed. Long-term follow-up with endoscopy is required.

Other gastric tumours

Gastrointestinal stromal tumours (GISTs)

These arise from the interstitial cells of Cajal, and their origin can be identified immunohistochemically by expression of the *c-kit* oncogene, which encodes the tyrosine kinase receptor. GISTs originate from the muscularis propria and submucosa. They are often found coincidentally at endoscopy, but may ulcerate and bleed. Tumour size, mitotic rate and presence of the *c-kit* oncogene predict malignant potential. Resection and chemoradiotherapy are traditional treatments. Recently, an antibody directed at the tyrosine kinase receptor has been used in malignant GISTs.

Gastric polyps

Hyperplastic or cystic fundal polyps are lesions of no clinical significance, whose only significance is to be differentiated from early gastric cancer. Rarely, adenomatous polyps are found. They are premalignant and associated with colonic polyps; they need resection and colonoscopic examination.

14

Small intestine

Malabsorption

Mechanisms

- Structural disorder (pancreas, small bowel, biliary tree).
- Mucosal disorder (pancreas, small bowel, biliary tree).
- Abnormal luminal digestion (metabolic defect).

Metabolic defects are unusual in causing isolated defects, whereas most other defects cause combined deficiencies (macronutrients – *carbohydrate, fat, protein*, or micronutrients – *vitamins, minerals*).

Clinical features

- **General**:
  - Malaise;
  - Anorexia, abdominal bloating;
  - Diarrhoea (especially stool bulk rather than frequency *cf* colonic disease);
  - Weight loss (document BMI).
- **Specific**:
  - Steatorrhoea = *fat malabsorption* (more severe in pancreatic disease than small bowel disease);
  - Oedema, ascites = *protein* malabsorption;
  - Paraesthesiae, tetany = Ca^{2+} or Mg^{2+} malabsorption;
  - Skin rash = Zn^{2+} or *vitamin B* malabsorption;
  - Cheilitis, glossitis = *vitamin B* malabsorption;
  - Neuropathy, psychological effects = *vitamin* B_{12} malabsorption;
  - Night blindness = *vitamin A* malabsorption;
  - Bruising = *vitamin K* or *vitamin C* malabsorption;
  - Bone pain, myopathy, osteoporosis = *vitamin D* malabsorption.

Investigations

Table 14.1 is an *aide memoire* to investigating the patient with suspected malabsorption. The intention is to:

- Establish the condition;
- Identify site of abnormality;
- Identify severity.

Intestinal failure

Sometimes called **short bowel syndrome**, this situation occurs when there is insufficient functioning small intestine to allow normal digestion and absorption. Typically, when there is < 100 cm of small bowel, malabsorption will occur (resulting in malnutrition and weight loss, as above); when the colon is also missing, severe dehydration and malabsorption occur. The stomach and intestine produce about 6 l of secretions, so reabsorption of this fluid is critical in intestinal failure.

Causes

- Extensive surgery.
- Crohn's disease.
- Mesenteric ischaemia.
- Radiation damage.
- Volvulus.
- *In children*, congenital abnormalities.

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Table 14.1 Potential investigations in patients with malabsorption. (malabsorption factor being assessed, if not obvious, given in parentheses).

	Condition	Cause
Serology	Full blood count Folate, B_{12}, iron studies INR (vitamin K) Albumin Ca^{2+}, Mg^{2+}	Coeliac antibodies Amylase is *not* a useful test of chronic pancreatitis* HIV antibody
Structural		Duodenal biopsy (see Box 14.1) Jejunal aspirate for *Giardia** Barium follow-through (to identify Crohn's disease, diverticula, stricture, tumours) Radiolabelled white cell scan (to identify Crohn's) Capsule endoscopy (to identify Crohn's disease, lymphangiectasia*) ERCP or MRCP (to identify chronic pancreatitis)
Functional	Faecal elastase (fat) – pancreas Xylose absorption (carbohydrate) – small bowel* 3. Faecal radioactivity after ^{131}I-albumin (protein) – small bowel*	Lactose hydrogen breath test – small bowel Glucose hydrogen breath test – small bowel bacterial overgrowth Schilling test – to detect small bowel disease* Basal acid output to identify Zollinger–Ellison*

*Rarely performed test.

Management

- **Short-term**:
  - Correct malnutrition (total parenteral nutrition);
  - Reduce gut secretions (loperamide, codeine and PPI).
- **Medium-term**:
  - Gradual reintroduction of enteral feeding.
- **Long-term**:
  - Monitor nutrition and ensure adequate calorie intake;
  - Monitor hydration status – especially if stoma output > 1.5l – and replace with oral rehydration solution;
  - Replace vitamins (B_{12}, D) and minerals (Ca^{2+}, Mg^{2+});
  - Reduce gut secretions (loperamide, codeine and PPI; rarely octreotide);
  - Treat small intestinal bacterial overgrowth (see p. 90);
  - Cholecystectomy if gallstones develop (greater risk due to bile acid depletion (see p. 122);
  - Small bowel transplantation (in very rare situations).

Coeliac disease

This is an immune-mediated disorder resulting in *small intestinal villous atrophy*, which *resolves on gluten withdrawal from the diet*.

Gluten is a family of proteins found in cereals (but not rice or oats), and the main toxic antigenic component of gluten is α-gliadin. This protein causes a T-cell-mediated inflammatory response of the small bowel. Prevalence in the UK is about 1:200 (least common in blacks and orientals), with a slight female preponderance. Estimates suggest that about 50% of cases are 'silent' (diagnosed on routine testing).

Clinical features

- **Infants**:
  - Diarrhoea;
  - Malabsorption;
  - Failure to thrive at weaning time.
- **Older children**:
  - Abdominal pain;
  - Anaemia;

- Short stature;
- Delayed puberty.

- **Adults**:
  - Abdominal bloating;
  - Lethargy;
  - Diarrhoea or constipation;
  - Iron-deficiency anaemia;
  - Occasionally malabsorption;
  - Rarely oral ulcers and psychiatric disturbance.

Coeliac disease is linked to HLA-DQ2, so is often associated with other autoimmune diseases (most commonly dermatitis herpetiformis [itchy blistering rash on extensor surfaces], insulin-dependent diabetes, thyroid disease, primary biliary cirrhosis [see Chapter 19], Sjögren's syndrome).

Investigations

- **Confirm diagnosis** (*condition*):
  - Duodenal biopsy – *gold standard for diagnosis* – villous atrophy (Box 14.1) *and* crypt hyperplasia *and* intraepithelial lymphocytosis (IEL; although seen in as many as 2% of routine small bowel biopsies, is present in 40% of coeliac patients);
  - IgA antibodies to tissue transglutaminase (TTG), endomysial and gliadin antigen (*Note*: false negative if patient has selective IgA deficiency). These are valuable *screening tests* and help *monitor treatment response*.
- **Look for consequences** (*complications*):
  - FBC (micro- or macro-cytic anaemia) and blood film (features of hyposplenism = target cells, Howell–Jolly bodies);
  - Haematinincs (low folate, B_{12}, iron status);
  - Clotting screen (vitamin K malabsorption);
  - Bone investigation (potentially low Ca^{2+}, vitamin D and albumin; osteopaenia on DEXA bone scan).
- **Supportive factors**: rarely needed (*coincidences*):
  - Liver enzymes (elevated transaminases);
  - Small bowel radiology (altered mucosal appearances, clumping of contrast);
  - Intestinal permeability (increased);
  - Faecal fat (increased due to fat malabsorption).

Box 14.1 Causes of villous atrophy.

Common
- Coeliac disease
- Dermatitis herpetiformis
- Giardiasis
- Acute infectious enteritis
- Bacterial overgrowth

Rare
- Lymphoma
- AIDS enteropathy
- Tropical sprue
- Hypogammaglobulinaemia
- Radiation enteropathy
- Whipple's disease
- NSAID enteropathy
- Lactose intolerance
- Zollinger–Ellison syndrome

Management

- Lifelong gluten-free diet (supported by dietician): this prevents the ongoing antigen provocation of the inflammatory response.
- Correct deficiencies (haematinics, vitamins and minerals).
- Aggressive management of any bone disease.
- If patient remains refractory:
  - Check compliance with diet; if compliant, consider immunosuppression;
  - Consider co-morbidity: giardiasis, lactase deficiency, microscopic colitis (see p. 99), IBS (see p. 100);
  - Consider complications: small intestinal bacterial overgrowth (common; see p. 90), small intestine T-cell lymphoma (rare; see p. 92), ulcerative jejunitis (very rare).

Tropical sprue

This extremely rare condition is associated with small intestine villous atrophy and is thought to be post-infectious. It affects primarily residents of (rather than travellers to) tropical countries. Diarrhoea and abdominal distension are common, and malabsorption may occur, especially if there is concomitant bacterial overgrowth. The main differential is giardiasis. Treatment is with long-term tetracycline and folic acid.

Table 14.2 Causes of small bowel bacterial overgrowth.

Site	Mechanism	Clinical condition
Stomach	Reduced gastric acidity	Gastric atrophy Partial gastrectomy Long-term PPI usage Old age
Small intestine	Structural abnormality	Small intestine diverticulosis Post Bilroth II surgery ('blind loop syndrome') Strictures (Crohn's disease)
	Abnormal communication between proximal and distal gut	Enterocolic fistula Ileocolonic resection
	Impaired motility	Systemic sclerosis Diabetic autonomic neuropathy Chronic intestinal pseudo-obstruction
	Altered immune function	Immunodeficiency syndromes
Miscellaneous		Liver cirrhosis Chronic pancreatitis

Small intestinal bacterial overgrowth

Colonisation of the small intestine by colonic flora results in their:

- Deconjugating bile salts (resulting in diarrhoea);
- Metabolising vitamin B_{12} (resulting in anaemia);
- Metabolising carbohydrate (resulting in calorie malnutrition and halitosis).

Small intestinal bacterial overgrowth almost always occurs secondary to another cause (Table 14.2).

Investigations

- **Condition**:
  - Jejunal aspirate – gold standard, but rarely required;
  - Hydrogen breath test after ingesting glucose or lactulose.
- **Cause**: small bowel radiology (to identify structural or communication abnormalities).
- **Complications**: – low B_{12} and normal folate.

Management

- Antibiotics directed towards colonic flora – may need repeated courses.
- Replace vitamin B_{12}.
- Definitive treatment if possible – surgery for structural abnormalities, prokinetics for motility disorders.

Bile acid malabsorption

A condition characterised by postprandial diarrhoea due to:

- Osmotic effect of bile salts in the colon;
- Steatorrhoea.

Bile acid malabsorption may be a primary abnormality, or if secondary, is most commonly due to Crohn's disease, ileal resection and intestinal failure.

A positive diagnosis depends on identifying reduced retention after administration of Se-HCAT (a synthetic radiolabelled bile acid analogue). Treatment is with cholestyramine, a bile acid sequestrant.

Whipple's disease

A rare disease characterised by malabsorption (see p. 87), a seronegative large-joint arthropathy, skin pigmentation, finger clubbing and fevers. It especially affects men.

Diagnosis is established by identifying 'foamy' macrophages which stain positive with periodic acid-Schiff (PAS) on jejunal biopsy. Electron microscopy may show the pathogenic actinomycete *Tropheryma whippelii*. Treatment is with co-trimoxazole or tetracycline for 1 year. One-third of patients relapse.

Protein-losing enteropathy

This is defined as gut loss of protein sufficient to reduce serum albumin. Patients therefore present with oedema in the absence of proteinuria or signs of heart failure,and in the presence of normal LFTs. Investigation is towards identifying the condition (faecal α-antitrypsin) and the potential cause (Table 14.3).

Intestinal infections

See Chapter 5.

Small intestine tumours

These are rare, accounting for < 5% of all GI tumours. Carcinoid and lymphoma are the two most important.

Carcinoid tumours

Carcinoid tumours are slow growing, and arise from the appendix (45%), small intestine (30%) or rectum (20%). **Carcinoid syndrome** occurs only if the tumour metastasises, occurring in 2% of cases with tumours > 2 cm in size. The carcinoid syndrome (Box 14.2) is caused by systemic release of serotonin, prostaglandins and bradykinins.

Diagnosis is made by measuring urinary 5-HIAA (a serotonin metabolite), although many tumours are detected incidentally at appendicectomy. Carcinoid tumours need surgical resection; carcinoid treatment implies hepatic metastases have occurred. Hepatic resection or arterial embolisation reduce metastatic mass of tumour and improve symptoms. Octreotide (a synthetic

Table 14.3 Conditions causing protein-losing enteropathy.

Mechanism	Site	Clinical condition	Comments
Mucosa intact	Stomach	Menetrier's disease	See p. 82
	Small intestine	Bacterial overgrowth	See p. 90
		Coeliac disease	See p. 88
		Eosinophilic gastroenteritis	Peripheral blood and mucosal/serosal eosinophilia in absence of parasite infection Treat with prednisolone or mast cell stabiliser (Na cromoglicate)
Mucosal ulcerated	Stomach	Cancer	See p. 85
	Small intestine	Cancer or lymphoma	See p. 91
		Crohn's disease	See p. 95
		Radiation enteritis	
	Colon	Ulcerative colitis	See p. 94
Lymphatic obstruction	Small intestine	Intestinal lymphangiectasia	Primary (congenital) or secondary (lymphatic obstruction)
		Lymphoma	Treat with low-fat diet and medium-chain triglycerides
		Whipple's disease	See p. 90
		Constrictive pericarditis	Causes back pressure on lymph vessels

Box 14.2 Clinical features of carcinoid syndrome.

History
- Flushing (provoked by alcohol and food)
- Diarrhoea
- Wheezing

Examination
- Facial telangiectasia
- Hepatomegaly
- Tricuspid and pulmonary valve stenosis

somatostatin analogue) may help palliate symptoms if debulking is not possible.

Lymphoma

These are rare tumours, but may complicate:

- Poorly managed coeliac disease (T-cell > B-cell tumours);
- AIDS and immunodeficiency states (B-cell > T-cell tumours).

Presentation is most commonly with obstructive symptoms, though haemorrhage or perforation may occur. Weight loss is common, but malabsorption syndromes are unusual. Abdominal CT scanning is usually diagnostic (luminal imaging is rarely required), and staging laparotomies are often required to decide treatment. Surgical resection is the treatment of choice, occasionally complemented with chemoradiotherapy.

Immunoproliferative small intestinal disease

A rare condition, also known as alpha heavy chain disease, this affects especially Mediterranean and Arab races. There is proliferation, ranging in severity from benign proliferation to malignant transformation, of IgA-producing small bowel immunocytes (in response to chronic bacterial antigen stimulation). There is a dense, diffuse proximal small bowel infiltration. Patients present typically as young adults with diarrhoea, malabsorption, clubbing and weight loss (differential diagnosis includes Crohn's and Whipple's disease). Serum electrophoresis shows α-heavy chains (the F_c portion of IgA) and hypo-γ-globulinaemia. Treatment is with long-term antibiotics, with only a minority of patients needing chemotherapy.

Polyps

- **Single polyps**: extremely rare, often malignant. May be secondaries from melanoma or lung.
- **Multiple polyps**: commoner. They are either:
  - Nodular lymphoid hyperplasia (in children, with hypo-γ-globulinaemia);
  - Hamartomas (Peutz–Jeghers syndrome, with labial pigmentation and intussusception);
  - Adenomatous (Cronkhite–Canada syndrome, with alopecia and nail dystrophy).

Adenocarcinoma

This is exceptionally rare, but may be associated with coeliac disease, Crohn's disease, Gardner's syndrome or familial adenomatous polyposis. It usually presents with obstruction or chronic blood loss, and surgical resection is the definitive treatment.

Miscellaneous intestinal disorders

Chronic intestinal pseudo-obstruction

This term refers to a spectrum of rare disorders characterised by the signs and symptoms of intestinal obstruction in the absence of true obstruction. It is caused by pathology of either gut smooth muscle ('visceral myopathy') or nerves ('visceral neuropathy') (Table 14.4).

In the early stages vomiting, abdominal distension and constipation occur episodically, with no symptoms between acute episodes. With disease progression, symptoms become more chronic and weight loss and malnutrition develop. Myopathic forms are commonly associated with urinary tract symptoms. The diagnosis requires radiological demonstration of a dilated proximal small bowel. Laparoscopic full-thickness biopsies of the small bowel confirm both the diagnosis and whether it is myopathic or neuropathic in origin.

Management comprises symptom relief during acute episodes, care being taken to avoid inducing opiate dependence. In the long-term parenteral

Table 14.4 Classification of chronic intestinal pseudo-obstruction. Those in bold have myopathic causation; others have neuropathic causation.

Primary	Secondary
Familial visceral myopathy	**Infiltrative – sarcoid, amyloid**
Familial visceral neuropathy	**Myopathic – mitochondrial disorders**
	Myenteric plexitis – inflammatory
	Myenteric plexitis – paraneoplastic (small cell lung cancer)
	CNS – disorders (Parkinson's, autonomic failure)
	Endocrine – hypothyroidism, porphyria

nutrition is often required and surgery should be avoided.

Meckel's diverticulum

This affects approximately 2% of the population, but is symptomatic in only 2% of those individuals. It is the commonest congenital gut abnormality, resulting from failure to close the vitelline duct. It is typically 60 cm (2 feet) proximal to the ileo-caecal valve and 5 cm (2 inches) long. If symptomatic, patients present before age 2, and males are twice as likely to be affected. Histologically, the mucosa is either gastric or pancreatic.

The classic symptoms are of painless melaena, with intestinal obstruction or intussusception being rare. Diagnosis is by a Meckel's scan (injecting a radioisotope which is taken up ectopic parietal cells). Surgical removal is rarely necessary.

Lactase deficiency

Brush border lactase digests lactose in milk to create glucose and galactose. Whereas Caucasians are very rarely deficient of the enzyme, 90% of Africans and Asians have hypolactasia. Secondary lactase deficiency may occur following gastroenteritides and if undigested lactose enters the colon, it becomes a substrate for colonic bacterial fermentation, causing an osmotic diarrhoea, flatulence, abdominal pain and borborygmi after eating milk products. Diagnosis is with a lactose substrate hydrogen breath test (see p. 49), and treatment is by minimising (not necessarily absolutely avoiding) milk products. Commercially available lactase may be added to the diet.

Food allergy

5% of children (cow's milk and soya especially) and 1% of adults (peanuts and shellfish especially) experience immune-mediated reactions to particular foods. Typically this is a type I hypersensitivity reaction and there is an instantaneous reaction on ingestion, which may be unpleasant but self-resolving. Rarely, there is a life-threatening anaphylaxis. Skin-prick tests and assay of serum IgE levels are not helpful in diagnosis, which rests on double-blind placebo-controlled food challenge. Treatment is by appropriate dietary avoidance and anaphylaxis may require constant availability of an epinephrine syringe.

NSAID-associated enteropathy

NSAID-induced erosions, ulcers, webs and strictures of the small bowel occur more often than NSAID gastropathy. These mucosal changes may result in bleeding and protein loss. While many of these are mild, the serious events (major haemorrhage, perforation, obstruction and sudden death) occur as often as that reported for NSAID gastropathy. The diagnosis of NSAID enteropathy has been greatly aided by the introduction of capsule enteroscopy.

15

Small and large bowel disorders

Inflammatory bowel diseases (IBDs)

These are a family of related diseases, which follow a relapsing and remitting course. They share the pathological hallmark of chronic inflammation, with environmental, genetic and immunological factors interacting to cause these diseases. The two major members of the family are Crohn's disease and ulcerative colitis.

Aetiology

Genetic factors

Twin studies have pointed to a *genetic predisposition* in a subset of IBD patients, specifically Crohn's disease (concordance ~50%, compared to ~10% for ulcerative colitis). In particular, the *CARD15/NOD2 gene* on chromosome 16 is linked to the development of Crohn's disease, probably by altering the way bacterial antigens are presented to the ileal mucosa. The disease is more common in Ashkenazi Jews and second-generation Asians in developed countries.

Environmental factors

The greatest prevalence of IBD is in developed countries, specifically where there is improved *sanitation*. It has been hypothesised that exposure to unhygienic conditions in early years can result in the development of intestinal immune defence mechanisms. S*moking* is another important factor, and curiously has contrasting effects in Crohn's disease and ulcerative colitis: increasing the risk of relapse in Crohn's and reducing the risk in ulcerative colitis.

Immunological factors

Recent evidence points to the role of the host bacterial environment in exerting a protective or stimulatory effect on the mucosal inflammation in IBD. This bacterial profile depends on early life factors (breast feeding, sanitation).

Epidemiology

The incidence of Crohn's disease, which is increasing, is ~7 in 100 000 in the developed world, with a prevalence of ~70 in 100 000. Unlike Crohn's, the incidence of ulcerative colitis is stable in the developed world, at ~12 in 100 000 with a prevalence of ~120 in 100 000. Both diseases show two age peaks, one in the third and fourth decades and the other in the sixth and seventh.

Pathogenesis

The gut tissue damage results from the interplay of circulating and gut immune cells (lymphocytes and neutrophils) and non-immune cells (mast cells and fibroblasts). It is clear that dietary antigens and host bacteria play a key initiating role in this inflammatory process. The antigens are taken up through breaches in the mucosa and specialised antigen-presenting cells (APCs) liberate a variety of pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α and

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interleukin-12 (IL-12). These APCs pass on the antigen to CD4+ T-lymphocytes (i.e. Th1 and Th2) which themselves then differentiate down specific pathways. **Crohn's disease** is predominantly a *Th1-driven* immune response, characterised initially by further release of pro-inflammatory cytokines, including TNF-α and interferon-γ. In contrast, **ulcerative colitis** is a *Th2-driven* immune response, with increased release of pro-inflammatory cytokines including IL-5.

Whichever immune process is followed, the net result is recruitment of further inflammatory cells (through increased adhesion of neutrophils to vascular endothelium) and activation of non-immune cells (mast cells, fibroblasts). This in turn results in tissue damage, and hence further ingress of antigen from the lumen into the gut mucosa.

Finally, in predisposed individuals, this inflammatory process can extend beyond the gut, resulting in the extraintestinal features of Crohn's disease and ulcerative colitis.

Distribution of disease

Although it can be difficult to differentiate Crohn's disease from ulcerative colitis, there are important differences in the distribution of the diseases.

Crohn's disease

Crohn's disease affects the gut in a *non-continuous* way, causing characteristic 'skip' lesions with normal mucosa in-between. Involvement is ileal or ileo-colonic (40%), small intestinal (30%), purely colonic (20%) and purely perianal (10%). In children, proximal gut inflammation is more common. Inflammation involves the *full thickness* of the gut wall with deep ulcers, causing a 'cobblestone' appearance. Ulcers may be so deep as to penetrate the bowel wall, causing fistulae and abscesses. The fistulae may be from the gut to adjacent viscera (bladder, vagina, other regions of the gut) or through the skin. The histological hallmark is of **giant cell granuloma**.

Ulcerative colitis

Ulcerative colitis always involves the rectum, and may extend in a *confluent* manner to involve the sigmoid colon and rectum (proctosigmoiditis) in 40%. About 20% have involvement of the entire colon (pan-colitis) and the remaining approximately 40% have an 'extensive colitis', which does not involve the whole colon but extends proximal to the sigmoid. Only the colonic mucosa is involved, and the inflammation is confined to the mucosa. Histologically, there is inflammation with **acute and chronic inflammatory cells** and **crypt abscesses**. Increased dysplasia with chronic inflammation predisposes to colorectal carcinoma.

About 35% of patients develop extraintestinal manifestations of IBD, and some (but not all) of these relate to the activity of disease in the gut (Table 15.1). HLA-B27 positivity predisposes to joint manifestations.

Clinical features

Crohn's disease

Characterised by **abdominal pain** and **diarrhoea**, but specific symptoms depend on the *region* of gut involved.

- **Ileal Crohn's** may cause small bowel obstruction and an inflammatory mass or abscess, resulting in abdominal pain (commonly post-prandial). This results in anorexia and coupled with non-bloody diarrhoea, weight loss is common. Inflammation of the small intestine may cause malabsorption, resulting in anaemia (classically B_{12} or folate deficiency) or malnutrition.
- **Proximal intestinal Crohn's disease** is more often associated with vomiting.
- **Crohn's colitis** presents with bloody diarrhoea, loss of mucus and constitutional symptoms (malaise and fever). In contrast to ulcerative colitis, which has similar symptoms, there is typically 'rectal sparing' on sigmoidoscopy.
- **Perianal Crohn's** may cause perianal soiling of mucus or faeces, and examination reveals skin tags, anal fissures or fistulous openings.

Ulcerative colitis

Characterised by *bloody diarrhoea*. Specific symptoms depend on the *extent* and *severity* of colonic involvement.

- **Proctitis** and **proctosigmoiditis** cause fresh rectal bleeding, loss of mucus per rectum and

Table 15.1 Extraintestinal manifestations of IBD.

System	Disorder	Relationship to disease activity?	Relationship with colonic involvement?	Relationship with Crohn's disease?
Ophthalmology	Conjunctivitis	+	+	
	Iritis/uveitis	+	+	
	Episcleritis/scleritis	+	+	
Oral	Aphthous mouth ulcers	+		+
	Angular stomatitis		+	
Dermatology	Erythema nodosum	+	+	
	Pyoderma gangrenosum	+	+	
	Erythema multiforme	+	+	
	Metastatic Crohn's disease	+		+
Musculoskeletal	Ankylosing spondylitis		+	
	Sacroiliitis		+	
	Peripheral arthropathy		+	
	Osteoporosis/ osteomalacia		+	+
Genitourinary	Kidney stones (oxalate)			+
	Amyloidosis			+
	Glomerulonephritis			
Hepatobiliary	Gallstones			
	Autoimmune hepatitis			
	Primary sclerosing cholangitis (PSC)		+	
	Cholangiocarcinoma		+	
	Fatty liver	+		
	Liver abscess	+	+	
Cardiovascular	Venous thrombosis	+		
	Pleuropericarditis			
Respiratory	Fibrosing alveolitis			
	Pulmonary vasculitis			
Neurology	Neuropathy			
	Myopathy			

tenesmus. Constitutional symptoms are absent unless *severe* inflammation occurs.

- **Extensive** or **pancolitis** present with more prominent constitutional symptoms, abdominal pain and bloody diarrhoea. *Severity* is indicated by bowel frequency (>6 per 24 h), degree of blood loss in stools, pulse > 90 bpm and temperature (>37.5°C).

In rare cases, the colon may dilate (**toxic megacolon**) with symptoms of a severe colitis, marked constitutional symptoms and abdominal distension. Because of the high risk of perforation, joint management between medical and surgical teams is essential. This complication can occur with Crohn's colitis, but is most frequent in first presentations of ulcerative colitis.

Cancer complicating colitis may occur with both ulcerative colitis and Crohn's disease. Risk is related to:

- Extent of disease (especially extensive UC);
- Duration of disease (>8 years);
- Comorbidity of primary sclerosing cholangitis (PSC);
- Coexistent family history of colorectal cancer.

The value of colonoscopic surveillance programmes looking for dysplasia is debated, but should certainly be considered with the latter two risks.

Small bowel adenocarcinoma is a very rare complication of extensive small bowel Crohn's disease.

Investigations

Investigations are directed towards confirming the condition (i.e. diagnosis, defining extent of disease and activity of disease), identifying cause (infection) and assessing for complications (toxic megacolon).

Condition

The differential diagnosis of small bowel Crohn's includes:

- Caecal carcinoma;
- Appendix abscess;
- Intestinal TB or lymphoma;
- Pelvic inflammatory disease;
- Radiation enteritis.

For colitis symptoms, the differential includes:

- Bacterial infections;
- Microscopic colitis;
- Colorectal carcinoma;
- Pseudo-membranous colitis diverticulitis;
- Ischaemic colitis;
- NSAID colitis;
- Radiation enteritis.

- **Lab tests**: anaemia, iron deficiency, leucocytosis, thrombocytosis, hypokalaemia, hypoalbuminaemia, ESR and CRP reflect disease activity. LFTs may be abnormal if PSC is present. *Clostridium difficile* toxin assay will exclude pseudo-membranous colitis.
- **Endoscopy**: sigmoidoscopy will identify an inflamed rectum in active ulcerative colitis (but may be normal in Crohn's colitis). In active disease the mucosa is friable and oedematous, and with more severe inflammation ulceration and mucopus are present. With chronic disease there is a loss of vascular pattern and a granular appearance of the mucosa. The key thing is to establish whether there is active mucosal disease, as if it is normal, the differential diagnosis needs to be considered. Thus, full colonoscopy is rarely needed in the acute setting; performed in the chronic setting, it informs about the extent of colonic ulcerative, and indicates whether there is terminal ileal Crohn's disease.
- **Abdominal X-ray**: essential if toxic megacolon is suspected (see below). In Crohn's ileitis it may show small bowel obstruction.
- **Barium studies**: these are *not* often required in the acute situation, but do have a role in defining the extent of disease (especially barium follow-through in Crohn's disease). Capsule endoscopy is rarely required, except in cases where small bowel changes may be too subtle for identification by barium or CT.
- **Radiolabelled white cell scan**: a less accurate assessor of areas of inflammation, best suited for patients too unwell to undergo endoscopy or abdominal CT (see below).

Cause

- Stool culture: as infective exacerbations are common

Complications

- **Abdominal X-ray**: in toxic megacolon, in addition to the colonic dilatation, there may also be mucosal oedema ('thumb-printing'), areas of necrosis ('mucosal islands') or evidence of perforation.
- **Abdominal ultrasound**: of value if an abdominal mass is suspected, and may also give information about bowel wall thickness (and hence activity).
- **Colonoscopy**: will identify colorectal cancer complicating chronic IBD.
- **Abdominopelvic CT or MRI**: invaluable acutely to identify colonic wall thickness, suspected perforation, extraluminal features of Crohn's disease. Pelvic MRI is particularly helpful for imaging perianal Crohn's disease.

Management

Crohn's disease

- **Inducing remission**:
  - Localised terminal ileal disease:
    - Medical first-line: course of oral prednisolone (>40 mg reducing over 4–6 weeks) or budesonide (a less well absorbed steroid, hence causing fewer side-effects);
    - Medical second-line either Methotrexate (intramuscular) at high dose for 12 weeks, or Infliximab infusion – this is a monoclonal antibody targeting TNF-αthat can induce rapid healing (beware adverse effects of severe infection, anaphylaxis and immune reaction);

Box 15.1 Characteristics of 5-ASA compounds. As 5-ASA is easily absorbed from small bowel, molecule needs modification to be released at site of inflammation.

Sulphasalazine	5-ASA linked to sulphapyridine (hence adverse effects) – well absorbed, so good for co-existent joint disease
Mesalazine	Coated and slow-release forms available, released according to luminal pH; used as oral and rectal preparations for colonic action
Olsalazine	Two 5-ASA molecules released in presence of colonic bacteria
Balsalzide	5-ASA molecule especially well released in distal colon

  - Surgical: limited ileal resection (may be preferred by patients as first-line therapy, and should be considered in all patients if frequent relapses occur; patients will need B_{12} replacement long-term).
- Extensive small bowel disease: careful parenteral nutrition is often needed:
  - First-line: delayed release oral 5-aminosalicylate (5-ASA) (Box 15.1);
  - Second-line: course of oral prednisolone;
  - Third–line: liquid diet and food exclusion diet.
- Colonic disease:
  - Proctitis or proctosigmoiditis – determine severity:
    Mild: 5-ASA or prednisolone suppositories;
    Severe: 5-ASA or prednisolone enemas; if refractory – course of oral prednisolone.
  - Extensive colitis – determine severity:
    Mild: high-dose oral 5-ASA
    Severe: course of oral prednisolone.
- Perianal Crohn's disease:
  - Fissure: topical gliceryl trinitrate and/or 5-ASA or prednisolone suppository;
  - Fistula: oral metronidazole or course of oral prednisolone; failing that, infliximab infusion or consideration of surgery ;

• – Abscess: surgical drainage. **Maintaining remission**:
- Localised terminal ileal disease:
  - Nothing may be needed, but if frequent relapses occur, consider:– High-dose oral 5-ASA, and if frequent relapses occur: – Azathioprine or 6-mercaptopurine (6-MP) – modulate the immune system over weeks, hence helpful in maintaining remission; beware adverse effects of bone marrow suppression and pancreatitis. These may be predictable in an individual by assay of level of the metabolising enzyme (TPMT);
  - An alternative to azathioprine or 6-MP is methotrexate (an immunosupressor with anti-inflammatory activity); beware liver and lung fibrosis.
- Extensive ileal disease: will usually need azathioprine or 6-MP.
- Colonic disease: same options as for maintenance of terminal ileal disease.
- Perianal disease: if frequent relapses or severe inflammation occur, then consider azathioprine or 6-MP.

Ulcerative colitis

• **Inducing remission**:
- Proctitis or procto-sigmoiditis – determine severity:
  - Mild: 5-ASA or prednisolone suppositories;
  - Severe: 5-ASA or prednisolone enemas:
    If remains refractory: course of oral prednisolone
    If still refractory: consider intravenous cyclosporin or infliximab or surgery (Box 15.2).
- Extensive colitis – determine severity:
  - Mild: high-dose oral 5-ASA;
  - Severe: course of oral prednisolone:
    If remains refractory: consider intravenous cyclosporin or infliximab
    If still refractory: surgery (Box 15.2).

• **Maintaining remission**:
- Proctitis or procto-sigmoiditis:
  - Mild cases may not need anything, or oral 5-ASA;
  - Severe cases may need azathioprine or 6-MP (for 2–4. years)
- Extensive colitis:
  - Mild: oral 5-ASA;
  - Severe: azathioprine or 6-MP.

Box 15.2 Operative options in ulcerative colitis.

Indications

- Failure of medical therapy (steroid dependence or drug side effects)
- Acute severe colitis and toxic megacolon
- Impaired quality of life
- Disease complications (severe haemorrhage, pyoderma gangrenosum)
- Colorectal cancer

Operations

- Proctocolectomy and ileostomy
- Proctocolectomy and ileoanal pouch (but 20% risk of this pouch becoming inflamed)
- Colectomy and ileorectal anastomosis (not favoured)

Osteoporosis

Crohn's disease patients in particular, and the use of steroids in all IBD, means patients are predisposed to metabolic bone disease. Diagnosis is with a DEXA bone scan. Treatment of mild cases is with calcium and vitamin D, and of severe cases is with bisphosphonates.

IBD in children, pregnancy and lactation

Maintaining nutrition is vital, to ensure normal puberty and growth (malnutrition is predisposed towards by chronic illness and treatments). For **Crohn's disease**, polymeric diets are preferred to steroids in children and adolescents to avoid growth retardation induced by the latter. Treatment with steroids, immunosuppression or surgery is otherwise similar to that in adults.

Pregnancy, labour and lactation are not associated with any greater risk of relapse. Equally, treatment options need not be altered by pregnancy or lactation.

Prognosis

Advances in medical and surgical treatment since the 1950s have resulted in life expectancy of IBD patients now being the same as the general population. About 90% of ileal Crohn's patients will have at least one operation, as opposed to only about 40% of colonic Crohn's patients. With ulcerative colitis, 90% will run a relapsing–remitting course, whilst 10% have chronic active disease, the latter being especially likely to undergo surgery. Surgery for ulcerative colitis is most common in the first 5 years after diagnosis.

Microscopic colitis

This term comprises two histologically distinct conditions, **collagenous colitis** and **lymphocytic colitis**. The incidence is 12 in 100 000, and is more common in patients with coeliac disease, autoimmune disorders and those taking drugs (particularly PPIs and NSAIDs). In both conditions, the endoscopic appearance of the mucosa is normal. Histologically, changes are seen more often on right than left colon biopsies: collagenous colitis is characterised by a thickened subepithelial collagen layer, whilst in lymphocytic colitis there is an increased infiltrate of intraepithelial lymphocytes.

Clinically, the hallmark is watery diarrhoea variably associated with abdominal pain and weight loss. Mild cases respond to loperamide used as required. For more severe cases, first choice is budesonide. Alternative options include oral 5-ASA, metronidazole or prednisolone.

Functional gastrointestinal disorders

This is a collective term for the spectrum of disorders labelled as functional heartburn, functional dyspepsia and irritable bowel syndrome (IBS). These are interrelated conditions involving the foregut, midgut and hindgut, respectively. All are marked by the complaint of pain associated with dysfunction of that region of the gut. They are common conditions (the most frequent disorders seen by gastroenterologists) with many overlapping symptoms, and up to 20% of the general population fulfil diagnostic criteria for these conditions. However, only about 10% present to medical services, women more often than men. Patients can present at any age, typically during childbearing years. Diagnosis is arrived at having

excluded organic diseases presenting with the same symptoms, typically blood tests (including testing for coeliac disease, see p. 19), endoscopy or radiology.

Not only do these patients show overlap between gut symptoms, but they also frequently report symptoms of functional disorders in other parts of the body (chronic fatigue syndrome, functional backache, etc.).

Aetiopathogenesis

The aetiopathogenesis of these disorders is multifactorial:

- **Psychological factors** contribute to the perception of gut stimuli and also influence gastric motility. This has been proven in both acute stress and in chronic depression and anxiety.
- **Visceral hypersensitivity and abnormal gut motility** are physiological phenomena that are often interrelated and contribute to causing gut symptoms. These visceral changes are in turn influenced by psychological factors. A variety of neurotransmitters have been implicated in these alterations of gut sensitivity and motility.
- **Alterations of mucosal immunology** function are also thought to contribute. About 25% of IBS cases begin after a gut infection, although again the risk of subsequently developing IBS is related to certain psychological traits. These patients with so-called postinfectious IBS have altered mast cell and cytokine function.

Clinical syndromes

- **Functional heartburn**: defined as the presence of a retrosternal burning sensation in the absence of pathological gastro-oesophageal reflux. Treatment is generally supportive, but a subset of patients may respond to intensive antireflux treatment, but antireflux surgery is not generally recommended.
- **Functional dyspepsia**: comprises two distinct subgroups: the postprandial distress syndrome (with postprandial fullness and early satiety) and the epigastric pain syndrome (chronic and less meal-related pain syndrome). PPIs are usually ineffective in this setting, treatment again being supportive. Cognitive behavioural therapy, where available, is effective.
- **Irritable bowel syndrome**: categorised as being either constipation-predominant (c-IBS), diarrhoea-predominant (d-IBS) or mixed stool pattern (m-IBS). The prevalence of these forms is approximately 40%, 20% and 40%, respectively. All forms have cramping abdominal pain as the central feature and symptoms do *not* occur at night. Associated symptoms of rectal mucus loss and incomplete evacuation are common. Treatment centres on making a positive diagnosis and offering empathic reassurance:
  - Diet is often of little help and probiotics remain unproven;
  - Antispasmodics may help some patients with postprandial cramp;
  - Tricyclic antidepressants in low dose are of proven efficacy;
  - Occasional patients need hypnotherapy or cognitive behavioural therapy.
- **Functional constipation** (see also p. 19). Constipation is a symptom, not a diagnosis. The cause needs to be investigated to exclude the exhaustive list of possible causes (see Table 3.3), but – in contrast to diarrhoea – in most cases a cause is not found, and the final diagnosis is of a functional disorder. The symptom is defined broadly: bowel opening < 3 times per week, or need to strain frequently, or passage of hard stools, or excessive time spent on toileting, or a sensation of incomplete voiding. With this loose definition, approximately 15% of the general Western population are said to be affected. Patients can be classified as having slow transit constipation, a defaecation disorder, or a combination of the two.
  - Slow transit constipation: mostly affects young women with characteristically infrequent urge, infrequent bowel opening and abdominal bloating. The colon is not dilated, and the diagnosis can be confirmed by a radio-opaque marker transit study. Specific management is to avoid a high-fibre diet and consider use of an osmotic laxative or, as required, stimulant laxative. Biofeedback may help toileting behaviour. Colectomy is almost never indicated.
  - Defaecation disorder: affects patients of all ages and is characterised by straining to evacuate the rectum, the need to use digital assistance to expel stool and a sensation of incomplete voiding. Diagnosis is confirmed by defaecography (barium or MR).

Management is with suppositories or enemas and biofeedback to improve defaecatory co-ordination. If proctography shows an anatomical abnormality, such as rectal prolapse or a rectocoele (a protrusion of the rectum into the posterior wall of the vagina), this may need surgical correction.

Ischaemia of the gut

The vessels supplying the foregut, midgut and hindgut are, respectively, the coeliac, superior mesenteric and inferior mesenteric. The former is the least vulnerable to ischaemia, and the 'watershed' area between the supply of the latter two (namely the splenic flexure of the colon) is the most vulnerable. Causes of gut ischaemia in order of frequency of occurrence:

- Arterial thromboembolism – by far the commonest;
- Venous insufficency (as part of a thrombophilic tendency);
- Profound hypotension;
- Vasculitis.

Acute small bowel ischaemia

This is a (rare) medical emergency, characterised by severe abdominal pain with minimal physical signs. In fact in the early stages, when the bowel is most salvageable, the only physical signs are abdominal distension and reduced bowel sounds. The features of the causative condition may be present (generalised atherosclerosis, atrial fibrillation, vasculitis). Epigastric bruits are diagnostic but rare. Rectal bleeding and peritonism are late, and often preterminal, features. Lab features are of a leucocytosis, raised amylase and metabolic acidosis.

Management is with aggressive resuscitation, analgesia and correction of acidosis. CT or mesenteric angiography may show the causative occlusion, but should not delay *early* laparotomy to resect infarcted gut. Mortality is over 80%, and long-term parenteral nutrition is often required in survivors due to the quantity of gut resected.

Chronic intestinal ischaemia

This is a rare condition, characterised by abdominal pain post-prandially in an arteriopathic patient. The pain typically starts 30 min after eating and continues for up to 4 h. Anorexia and weight loss are the sequelae to this meal-related pain. Epigastric bruits are rarely heard.

A variety of radiological techniques are available to image the intestinal arteries. The gold standard is angiography, but less invasive options include duplex ultrasound, CT and MR angiography. Angioplasty or arterial reconstruction is rarely appropriate in these patients who often have major atherosclerotic comorbidity. Small frequent meals are advised.

Ischaemic colitis

This is a condition which affects arteriopathic individuals The typical symptoms are abdominal pain (unrelated to meals), rectal bleeding and occasionally diarrhoea. A more severe, and rarer, fulminant form of the condition may occur, with toxic dilatation and a gangrenous colon.

Abdominal X-ray may show mucosal oedema ('thumb-printing') at the splenic flexure, and a gentle limited colonoscopy may show erythematous and ulcerated mucosa. Biopsy findings of haemosiderin-laden macrophages are diagnostic. Management is by resuscitation and early enteral nutrition support. The prognosis is usually excellent, although colonic strictures may develop later in some patients.

Radiation enterocolitis

Acute radiation enteritis

This affects about 70% of patients in the early weeks after first radiotherapy. Symptoms of vomiting, pain and diarrhoea are usually self-limiting.

Chronic enteritis

Approximately 15% of patients undergoing abdominal or pelvic radiotherapy sustain damage to the gut, the risk depending on cumulative dose and site of exposure. Typically symptoms begin within 12 months of exposure, but may first present 20 years later. The pathology is of an obliterative endarteritis with secondary fibrosis. The latter results in ischaemia, and hence ulceration, perforation, fistulisation or stricturing.

A variety of symptom patterns may occur:

- **Recto-sigmoid**: rectal bleeding, tenesmus, rectal pain and loose stools. Sigmoidoscopy reveals friable, inflamed mucosa, with telangiectatic bleeding. Management of rectal bleeding is with argon plasma coagulation of involved mucosa. Topical 5-ASA compounds, prednisolone, sucralfate and even formaldehyde have all been used. Hyperbaric oxygen may be considered in refractory cases. Surgery is avoided.
- **Faecal incontinence**: the internal anal sphincter is especially vulnerable to ionising radiation, and passive faecal soiling should be managed with loperamide and if needed anal plugs.
- **Diarrhoea** may result from bacterial overgrowth in blind segments formed by strictures or bile salt malabsorption, treated respectively by antibiotics or cholestyramine. A rarer cause of diarrhoea is small bowel fistulae managed by nutritional support and loperamide; surgery is again best avoided.

Prevention of damage is the best treatment. Optimising dose and radiation dosing regimens is critical. Surgical lifting of bowel loops out of the field of radiation, with or without use of bioprotective mesh, is used when heavy localised exposure cannot be avoided.

16

Colon

Colorectal tumours

Colonic polyps

These may be classified histologically as neoplastic or non-neoplastic, but cannot be distinguished endoscopically with certainty.

- Neoplastic polyps:
  - Adenoma.
- Non-neoplastic polyps:
  - Hamartoma;
  - Metaplastic ('hyperplastic');
  - Inflammatory.

Colonic adenomas

All colonic adenocarcinomas originate from colonic adenomas, but only a small minority of adenomas are premalignant. 30% of people in the UK develop an adenoma by age 60 and 3% have a lifetime risk of colorectal cancer. The progression from adenoma to carcinoma takes on average 10 years. Adenomas are classified by endoscopic and histological (Box 16.1) appearance:

- Endoscopic:
  - Pedunculated;
  - Sessile;
  - Flat.
- Histological:
  - Tubular;
  - Villous;
  - Tubulo-villous;
  - Serrated ('saw-tooth' histology).

Adenomas are usually asymptomatic, detected on surveillance or endoscopy. Occasionally they may bleed, and very rarely villous adenomas cause a mucous diarrhoea.

Colonoscopy and removal of polyps is the gold standard (though it is estimated that 25% of polyps are missed by an average colonoscopist). Histology should determine the histological classification and completeness of removal. The need for, and timing interval of, future colonoscopy is dependent on the malignant potential of the polyps(s). Complications of polypectomy are:

- 2% early haemorrhage;
- 2% delayed (up to 2 weeks) haemorrhage;
- 0.5% perforation;
- 30% recurrence of polyp at same site (incomplete removal).

Inherited polyposis syndromes

Familial adenomatous polyposis (FAP)

FAP is an uncommon disorder characterised by multiple (>100) colonic adenomas which invariably progress to colorectal cancer unless colectomy is performed in the second or third decade of life. It accounts for 1% of colorectal cancers. The cause is a chromosomal (autosomal dominant) disorder arising from a mutation in the *APC* gene (chromosome 5); about 25% of cases are spontaneous new mutations with no family history. Gastric and duodenal adenomas and carcinomas also occur

Lecture Notes: Gastroenterology and Hepatology, 1st edition. Anton Emmanuel and Stephen Inns.

Box 16.1 Histological features defining malignant potential of an adenoma.

- Size (especially > 2 cm)
- Multiplicity of polyps (>5)
- Histological type (villous > tubulo-villous > tubular > serrated)
- Histological degree of dysplasia

Box 16.2 Amsterdam criteria for diagnosing HNPCC.

- ≥ One HNPCC-related cancer diagnosed < age 50
- ≥ Two generations with colorectal cancer
- ≥ Three family members with HNPCC-related cancers, at least one being a first-degree relative

with greater frequency. **Gardner's syndrome** is a variant associated with osteomas.

The cornerstone of management is early diagnosis and family screening by colonoscopy from teenage years until the age of 40. When polyps are detected pan-proctocolectomy is the treatment of choice, with formation of an ileoanal pouch or end ileostomy. Carcinoma of the ampulla should be screened for, and abdominal pain after colectomy should raise the concern of intra-abdominal desmoid tumours.

Hereditary non-polyposis colorectal cancer (HNPCC)

This autosomal dominant disorder accounts for 10% of colorectal cancers, and is caused by germline mutations of mismatch repair genes. Primarily right-sided colon cancer develops at a mean age of 45, without the generalised polyposis of FAP, although almost half of patients have metachronous lesions. There is an increased risk of other adenocarcinomas (uterus, ovary, stomach and small bowel).

Management centres on family screening-based Amsterdam criteria (Box 16.2), undertaken by gene testing. Microsatellite instability is a histological feature of HNPCC tumours, and its finding should trigger consideration of HNPCC. Surveillance upper and lower gastrointestinal endoscopy is required.

Hamartomas

There are specific syndromes in which hamartomatous polyps occur. These syndromes are often associated with greater risk of non-gut cancers (breast, thyroid):

- **Peutz–Jeghers syndrome**:
  - Multiple small hamartomas in small bowel *and* colon;
  - Buccal and labial melanin pigmentation;
  - Autosomal dominant inheritance; Hamartomas are usually asymptomatic, but may rarely bleed or form the focus of intussusception.
  - **Juvenile polyposis**: Large pedunculated vascular polyps in small bowel *and* colon;
  - Specific gene mutations with autosomal dominant inheritance;
  - Colorectal cancer risk of ~40%, gastric cancer risk of ~20%;
  - Treatment is with endoscopic polypectomy if there are a few polyps, but with heavy polyp density, colectomy is recommended. Family screening for the gene mutation should be performed.
- **Cowden's disease**:
  - Gastric, small bowel and cutaneous hamartomas;
  - Autosomal dominant inheritance;
  - Multiple congenital abnormalities.
- **Cronkhite-Canada syndrome**:
  - A non-inherited disorder;
  - Diffuse gastrointestinal hamartomas (including gastric);
  - Malabsorption;
  - Alopecia and nail dystrophy.

Metaplastic polyps

Extremely common, usually small (< 5 mm) polyps found in the rectum.

Inflammatory polyps

Known as 'pseudo-polyps' since they represent exuberant mucosal regrowth after a severe episode of colitis.

Colorectal adenocarcinoma

This is the second commonest cancer in the UK, with 30 000 cases per year, two-thirds of which result in death. The majority (75%) are sporadic,

10–12% occur in relation to the inherited polyposis syndromes (see p. 94), 10% have some other family history and 2% are related to inflammatory bowel disease (IBD).

Aetiopathology

The adenoma–carcinoma sequence (Figure 16.1) is widely accepted as the mechanism resulting in all but IBD-related colorectal cancers:

- **Risk factors**:
  - Genetic (as per sequence above);
  - Dietary:
    - Exacerbating – red meat, saturated animal fats;
    - Protective – dietary fibre (cereal and fruit/vegetable), folic acid.
  - Chronic inflammation (IBD [see p. 94], prior ureterosigmoidostomy);
  - Medical conditions (primary sclerosing cholangitis, acromegaly, obesity);
  - Smoking.
- **Location**:
  - 65% rectosigmoid;
  - 10% left and transverse colon;
  - 25% right colon;
  - (Note 5% are synchronous);
  - Spread occurs early through bowel wall, then into lymphatics, and later by portal and systemic circulations.

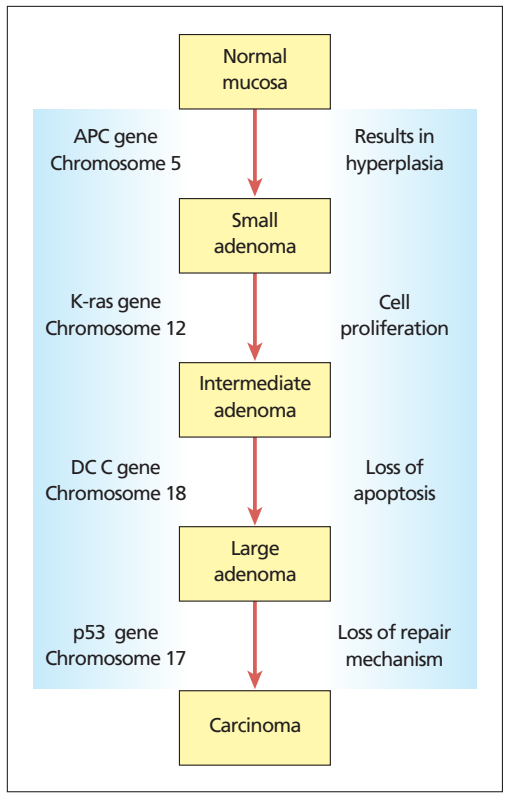

Figure 16.1 Adenoma–carcinoma sequence. *APC*, adenomatous polyposis coli; *DCC*, deleted in colon cancer (this *DCC* gene has the least strong evidence of involvement in this sequence).

Clinical features

Depend on location of the tumour:

- Rectal bleeding, rectal and left colon tumours (remember that presence of haemorrhoids does not preclude the possibility of comorbid cancer);
- Altered bowel habit – especially in distal tumours;
- Anorexia, weight loss, abdominal mass and anaemia – especially caecal cancers;
- Intestinal obstruction or perforation is rare – especially in distal tumours;
- Tenesmus – in rectal cancers;
- Abdominal pain – a non-specific symptom.

Investigations

- **Condition**:
  - Rigid sigmoidoscopy (will detect 30% of tumours);
  - Flexible sigmoidoscopy – for any patients with fresh rectal bleeding.
  - Colonoscopy if:
    - Altered bowel habit;
    - Polyps seen at flexible sigmoidoscopy;
    - Family history of colorectal cancer;
    - Surveillance of IBD or polyps; endoscopic examination allows histological specimens to be collected.
  - Barium enema: apple-core strictures or ulcerated defects may be seen, but sensitivity is less than with colonoscopy;
  - CT colonography ('virtual colonoscopy'): more comfortable than colonoscopy; but does involve radiation exposure, bowel preparation is still needed, histology is not possible and resolution is less than with colonoscopy;
  - FBC and iron studies: supportive of diagnosis;
  - Serum carcinoma embryonic antigen (CEA): of supportive value, but note false positives and negatives are not infrequent.

Table 16.1 Dukes' staging for colorectal cancer.

Dukes' stage	Description	Prevalence at diagnosis (%)	5-year survival (%)
Dukes' A ($T_{1–2}$, N_0, M_0)	Tumour confined to bowel wall	10	95
Dukes' B ($T_{3–4}$, N_0, M_0)	Tumour extends through bowel wall	35	75
Dukes' C (T_{any}, N_1, M_0)	Tumour through bowel wall and involves lymph nodes	35	35
Dukes' D (T_{any}, N_{either}, M_1)	Distant metastases	20	1

Table 16.2 TNM staging for colorectal cancer.

Stage	Description
T – primary tumour	T_0 – no evidence of tumour $T_{1–4}$ – varying depths of invasion
N – lymph nodes	N_0 – no nodes N_1 – positive nodes
M – metastases	M_0 – no metastases M_1 – metastases

- **Complications** staging:
  - LFTs;
  - CT abdomen: for local spread and liver metastases;
  - Pelvic MRI: needed for staging of rectal cancers.
- **Staging**:use of Dukes staging and TNM staging systems (Tables 16.1 and 16.2)

Management

Decided at multidisciplinary team (MDT) meetings.

Surgery

Suitable for Dukes' A and B tumours.

- **Basic principles**:
  - Tumour resection;
  - Direct anastomosis if possible;
  - Clear resection margins;
  - Sampling of lymph nodes.
- **Rectal cancers**: total mesorectal excision reduces recurrence; cancers within 2 cm of the anus require abdominoperineal (AP) resection and colostomy

Adjuvant therapy

This may be pre- or post-operative, by radiotherapy or chemotherapy.

- **Colon cancer**:
  - Chemotherapy (5-fluoro-uracil or irinotecan) for Dukes' C or B with T_4;
  - Radiotherapy is only used for palliation.
- **Rectal cancer**:
  - Preoperative radiotherapy or chemoradiotherapy is used for Dukes' B and C cancers to downsize the tumour and improve postoperative survival;
  - Postoperative chemotherapy is also widely employed.

Palliation

- **Surgery**:
  - To treat obstruction, intractable bleeding or pain;
  - Liver resection of metastases.
- **Chemotherapy or radiotherapy**:
  - Sometimes used for tenesmus, pain.
- **Endoscopy**:
  - Laser therapy for bleeding;
  - Expandable metal stent insertion for obstruction in a non-resectable patient.

Prognosis

This depends on the cancer stage at presentation: 5-year survival for Dukes A is > 90%, for Dukes B is 77%, for Dukes C is 48% and for Dukes D is 6%. Survival rates are halved if patients present with obstruction.

Prevention

Intention is to detect and destroy lesions at a pre-malignant stage:

- Faecal occult blood test (FOBT): performed every 1–2 years after age 60 in the UK, increases the proportion of early cancers detected and reduces mortality by 16%;
- Flexible sigmoidoscopy: more invasive, reduces mortality by 35%;
- Colonoscopy: gold standard, but impractical as a screening test;
- Faecal and blood gene mutation testing is not yet sensitive enough to be considered at this time.

Surveillance

- Colonoscopy 6–12 months after colon cancer resection to detect metachronous lesions.
- CT scan of the abdomen to identify resectable liver metastases.

Chemoprevention

- Aspirin reduces risk of recurrent adenomas after colorectal cancer surgery by 35%; COX-2 inhibitors are not indicated.
- Optimising calcium and folic acid intake are generally recommended.

Miscellaneous colonic disorders

Colonic diverticular disease

Colonic diverticula increase in prevalence with age, and are most common in the developed world. 50% of over 50 year olds have 'diverticulosis', which is asymptomatic diverticula. In the Western world, diverticula are most prevalent in the sigmoid and left colon, whilst in Oriental populations and the rare under 40 year old who develops them, right-sided disease is commoner. Diverticula never occur in the rectum. The term 'diverticular disease' refers to patients having symptomatic diverticula, and 'diverticulitis' refers to diverticula causing complications (bleeding, inflammation, stricturing, perforation). The relationship between these terms is shown in Figure 16.2.

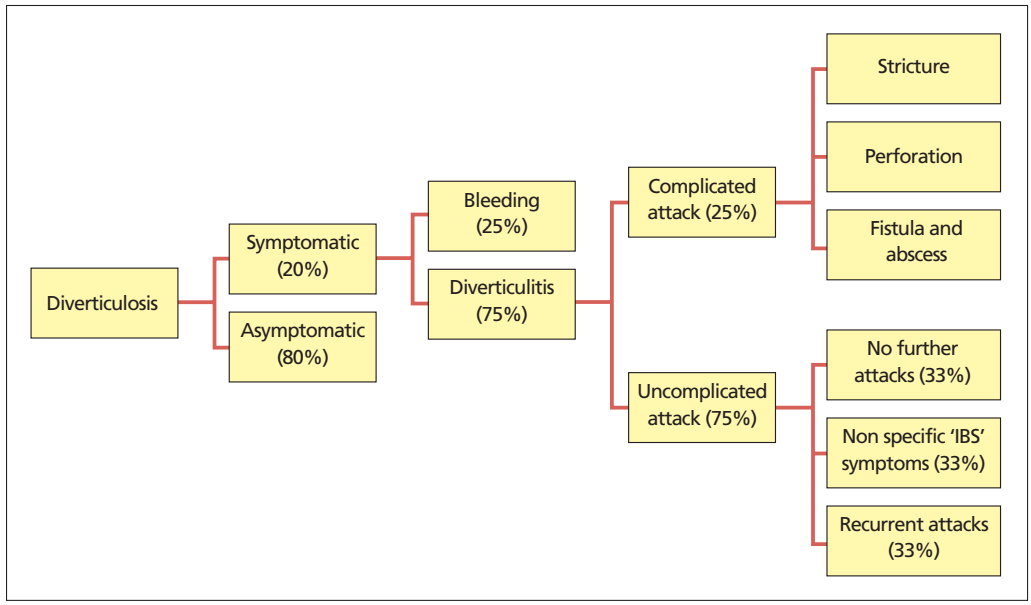

Figure 16.2 Possible presentations with colonic diverticula. IBS, irritable bowel syndrome.

Aetiopathogenesis

A diet, especially in early life, which is low in unrefined fibre is the traditional explanation of diverticulosis and explains the geographical variability of the problem, and the changes seen with epidemiological studies of migrant populations. With a low-fibre diet, the resulting stools are small volume and require greater colonic pressure for propulsion, explaining the circular muscle hypertrophy seen in diverticula. The elevated pressures result in mucosal herniation between taenia coli muscles of the colon. Faeces may impact in the neck of these diverticula, resulting in inflammation, which may either spontaneously resolve or more rarely lead to haemorrhage, perforation, etc.

Clinical syndromes

- **Uncomplicated diverticulosis**: symptoms of colicky left iliac fossa pain eased by defaecation, passage of pellet stools and abdominal bloating are typical. The possibility of colorectal cancer always requires exclusion in view of the prevalence of diverticula. Colonoscopy is diagnostic and helps exclude other lesions, but carries the small risk of perforation. Rigid sigmoidoscopy with histology and a barium enema is an alternative strategy. Treatment is by increasing dietary fluid and fibre intake, hence improving stool output and preventing further diverticula formation.
- **Diverticular bleeding**: there is often right-sided bleeding, so visible blood loss may not occur. Greatest risks are in elderly men and those taking NSAIDs or warfarin. Most settle with simple observation. Major haemorrhage occurs in about one-third of cases, and rebleeding rates increase with time and number of prior bleeds. Nevertheless, anaemia and altered bowel habit should *not* be assumed to be due to diverticula until cancer and IBD have been ruled out.
- **Diverticulitis**: characterised by pain, fever, raised white count and inflammatory markers ('left-sided appendicitis'). Colonoscopy is contraindicated acutely, but a CT will demonstrate any abscess:
  - *Mild cases* are managed with oral antibiotics (metronidazole and a cephalosporin or ciprofloxacin) and analgesia;
  - *Severe cases* may need hospitalisation for intravenous antibiotics;
  - *Complicated attacks* (stricture, perforation, fistula, abscess) require surgery. Fistulation (to bladder or vagina) occurs in 20%; mortality following perforation is high;
  - *Uncomplicated attacks* only need consideration of elective surgical therapy if there is:
    - Localised diverticula;
    - Frequent recurrence;
    - Episodes beginning at a young age (known to run a more recurrent course).

Megacolon

Congenital (Hirschsprung's disease) and acquired (idiopathic megacolon and megarectum) forms are recognised.

Hirschsprung's disease

Caused by congenital aganglionosis of the colon, resulting from defective migration of neuroblasts into the embryonic hindgut. It is a rare cause of constipation and a family history is present in 35% of cases; some hereditary causes are associated with a specific gene mutation (*RET* tyrosine kinase).

The absence of submucosal ganglia is usually localised to the distal rectum, but may be widespread in the hindgut (sigmoid colon). This results in defective anorectal reflexes, in particular the absence of the internal anal sphincter relaxation in response to rectal filling ('rectoanal inhibitory reflex'). This results in constipation, abdominal distension and vomiting; most cases present in neonatal life, although up to 10% present in adolescents and adults. Diagnosis is established by demonstrating the absence of the rectoanal inhibitory reflex on physiological testing (*condition*). In addition, barium enema will show the narrowed aganglionic segment and dilatation proximal to that. The *cause* may be identified through surgically-obtained full thickness biopsies of the rectum and appropriate immunohistochemistry. Treatment involves resection of the localised segment.

Idiopathic megacolon and megarectum

This condition may be localised to the rectum or may more extensively involve the colon. Constipation with infrequent urge to defaecate is common to both megarectum and megacolon, but the former is more often associated with faecal soiling. Faecal impaction and overflow incontinence is the main complication. In children, it is

thought to result from disturbed toileting behaviour in toddlers, with voluntary avoidance of toilets and withholding of stools. The differential is with Hirschsprung's disease, from which it is distinct due to:

- Absence of a lifelong history;
- Frequent report of faecal soiling (which does not occur in Hirschsprung's); Presence of stool in the rectum on digital examination.

Adult megacolon may be associated with dementia or depression, scleroderma, chronic opiate use and neurological disorders like multiple sclerosis. Diagnosis is confirmed by unprepared contrast study demonstrating continuous colonic dilatation until a point of abrupt transition to proximally normal diameter colon (*Note*: by contrast, in Hirschsprung's, the colon proximal to the narrowing is dilated). Management is by titrated use of osmotic laxative with or without enemas to empty the rectum. Surgical resection of the dilated colon is required only in a minority of laxative-refractory patients. The cornerstone is to avoid faecal impaction and overflow.

Acute colonic pseudo-obstruction ('Ogilvie's syndrome')

Characterised by sudden, painless distension of the colon in the absence of mechanical obstruction. It is often due to disturbance of the retroperitoneal autonomic nerves (e.g. secondary to abdominal surgery, retroperitoneal tumour invasion, abdominal trauma, diabetic autonomic neuropathy). It may occur secondary to metabolic disturbance (e.g. electrolyte disturbance, uraemia, respiratory failure). Examination reveals abdominal distension and increased bowel sounds. The *condition* is confirmed by plain abdominal X-ray showing the dilated gut and contrast study will exclude a mechanical cause of obstruction.

Management depends on reversing the cause if possible. The parasympathomimetic neostigmine may help to deflate the colon and ease symptoms. If urgent decompression is required (due to the risk of perforation with gross colonic distension), then a rectally placed flatus tube or careful colonic decompression are preferable to surgical caecostomy.

Pneumatosis cystoides intestinalis

A rare condition with multiple gas-filled submucosal cysts in the colon (and rarely small bowel). It is usually asymptomatic, but diarrhoea, rectal bleeding and pain may occur. The cysts may be seen on abdominal X-rays or lower GI endoscopy. If treatment is required for severe symptoms, 70% inspired oxygen for 5 days via a mask and rebreather gives long-term benefit. Elemental diets may also help.

17

Anorectum

Haemorrhoids

These are commonly occurring dilatations of anal veins surrounded by tissue. *Internal* haemorrhoids originate above the dentate line, and comprise a venous branch of the internal haemorrhoidal plexus surrounded by rectal mucosa. *External* haemorrhoids arise below the dentate line and comprise a branch of the inferior venous plexus overlain by anal skin. Over half the population has haemorrhoids, being especially common in situations where there is raised intra-abdominal pressure (chronic constipation, pregnancy, chronic cough).

Haemorrhoids most commonly present with the sensation of a lump at the anus. They are classified as:

- First-degree: internal haemorrhoids move into the anal canal;
- Second-degree: haemorrhoids prolapsed out of the anus on straining, but spontaneously reduce;
- Third-degree: as second-degree, but need manual reduction;
- Fourth-degree: as second-degree, but cannot be reduced.

The other classical presentation is with rectal bleeding, typically in small quantities of fresh blood on the toilet tissue. Rarely, haemorrhoids may:

- Cause passive faecal or mucus leakage (and hence pruritus ani);
- Thrombose (causing severe pain).

Diagnosis is usually obvious on anal inspection and asking the patient to gently strain. If no lump is visible, anoscopy may be required.

Management (Table 17.1)

First- and second-degree haemorrhoids will usually respond to non-surgical approaches as an outpatient, whereas third- and fourth-degree piles usually need haemorrhoidectomy.

Anal fissure

This is a tear of the skin of the anal canal. It occurs most commonly in young adults, affecting men and women equally. Typically they occur in the posterior midline where anal blood flow is lowest and the anal skin is least supported. Internal anal sphincter spasm also contributes to the development of an anal fissure.

They occur most often in patients with:

- Constipation (by far the commonest cause);
- Crohn's disease;
- Anorectal infection (TB and HIV patients);
- Haematological malignancy.

Clinical features

Fissures present with pain which begins with defaecation but then continues afterwards. Blood loss is common, but not invariable. The diagnosis is evident on inspection, but examination can be very uncomfortable for the patient. Typical features are:

- Breach in the anal skin;

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Table 17.1 Management of haemorrhoids.

General	Non-surgical	Surgical
Correct constipation (especially with diet alteration or bulk laxatives)	Rubber band ligation (complications: pain, bleeding, infection)	iStapled' haemorrhoidectomy – with a mini bowel anastomosis device (complications: pain, incomplete excision)
Avoiding straining	Injection sclerotherapy (complications: infection, ulceration)	Open haemorrhoidectomy (complications: pain, anal stenosis, infection)
Local anaesthetic suppositories or creams	Photocoagulation (complications: pain, ulceration)	

Table 17.2 Management of anal fissure.

First-line	Second-line	Third-line
Correct constipation (especially with diet alteration or bulk laxatives)	Topical nitroglycerin or diltiazem	Botox injection
Avoiding straining		
Local anaesthetic suppositories or creams		

- 'Sentinel' pile (actually a skin tag that grows near the fissure);
- Muscle fibres of the internal sphincter (with severe fissuring).

Management

Treatment options are listed in Table 17.2.

Internal anal sphincterotomy surgery is reserved for refractory fissures only, due to the risk of faecal incontinence.

Anal fistula

A fistula is a pathological connection between the gut and skin, in this situation, the anal canal and perianal skin. They occur more often in men and typically in the third and fourth decades.

At-risk groups:

- Crohn's disease;
- Prior anal surgery;
- Prior pelvic radiation;
- Prior pelvic trauma.

Clinical features

Typically there is anal discomfort or itching. Loss of faecal material and pus are more common than bleeding.

Investigations

Inspection reveals the external opening whilst endoscopy rarely identifies the internal one. MRI and endoanal ultrasound are essential to help identify the internal sphincter tracks prior to surgery. Classification is based on whether:

- Track crosses the sphincters (trans-sphincteric), is in-between them (inter-sphincteric) or outside them (extrasphincteric); or
- Internal opening is above (high) or below (low) puborectalis muscle

Management

The principles of surgery are to obtain drainage of all fistulae and to lay open or cut out the tracks to stop them spreading and causing further fistulae. Rarely, a defunctioning stoma may be needed to cover a complex fistula repair.

Anal pain and itch

Anal pain can be caused by a number of organic conditions:

Table 17.3 Clinical features and management of conditions causing anal pain.

	Proctalgia fugax	Levator ani syndrome	Pruritus ani
Type of pain	Episodic, intense	Episodic, intense	Itch around anus
Duration of pain	Seconds (<20 s)	Minutes (<30 min)	Chronic (worse at night)
Epidemiology	Males especially, under 40 s	Females especially, over 40 s	Males especially
Associated symptoms	Faecal urgency, syncope	Difficult evacuation	Depend on cause (see below)
Digital examination	Normal tone, painless.	Sphincter spasm and pubo-rectalis tenderness	Exclude worms or candida Look for eczema and psoriasis
Treatment	Explanation and reassurance Acute treatment with inhaled salbutamol or topical GTN Chronic treatment with diet or psychotherapy	Explanation and reassurance Pelvic floor physiotherapy and sitz baths	Explanation and reassurance Avoid scratching and over-zealous cleaning Increase diet fibre and use wet-wipes Local anaesthetic cream

- Perianal Crohn's disease (see p. 95);
- Anal fissure;
- Thrombosed haemorrhoids (see p. 110);
- Radiation proctitis (see p. 101);
- Anorectal abscess (following blockage of an anal gland).

In addition, there are functional conditions that can cause anal discomfort (Table 17.3).

Anal cancers

Histologically, a variety of cancers may arise. Most patients present in their fifth or sixth decades. Anal carcinoma occurs with the greatest frequency, the rest are rarer:

- Anal carcinoma (of which there are three subtypes: transitional epithelium, squamous epithelium or keratinised perianal skin);
- Anal adenocarcinoma;
- Basal cell carcinoma;
- Bowen's disease;
- Perianal Paget's disease;
- Malignant melanoma.

Particular at-risk groups for **anal carcinoma** include:

- HIV infection
- HPV (human papilloma virus) infection
- Syphilis
- People participating in anoreceptive intercourse
- Prior perianal Crohn's disease or fistulae
- Prior pelvic irradiation
- People who have received immunosuppression
- Smokers

Investigations

Diagnosis often requires examination under anaesthesia and biopsy.

Management

Treatment depends on size of lesion:

- Involving mucosa/submucosa only: wide local excision;
- More advanced lesions: abdominoperineal resection.

Combination chemotherapy and radiotherapy may sometimes be added.

Rectal prolapse

This occurs most frequently in women over the age of 50 who have had children. Other *at-risk groups* include:

- Patients who chronically strain;
- Patients with cystic fibrosis (where it can occur in childhood);
- Spina bifida;
- Congenital mesenchymal disorders (e.g. Marfan's syndrome).

In the early stages there is prolapse of the mucosa only and in more severe forms the whole rectal wall is externalised (and very rarely may be life-threateningly incarcerated). Patients usually present with the sensation of a mass on wiping. They may passively soil stool, but blood loss and pain are rare.

Examination while straining will reveal the prolapse, and this may need to be done with the patient seated on the toilet.

Management

Mild forms may be managed by biofeedback to retrain defaecatory co-ordination. More severe prolapse will need surgery, which can be transanal, perineal or transabdominal.

Solitary rectal ulcer syndrome

Mucosal ischaemia and ulceration resulting from repeated straining, anal self-digitation and rectal prolapse causes loss of blood and mucus per rectum. It typically occurs in young women, and there will often be a prior history of constipation and psychological distress. The condition is easily identified at sigmoidoscopy with single or multiple ulcers, typically on the anterior rectal wall, in the distal 10 cm.

Management

Treatment is initially through biofeedback, to avoid straining and digitation. Laxatives may be needed, but suppositories and enemas are best not used to avoid the cycle of recurrent digitation. Rarely, surgical therapy may be needed, especially if heavy bleeding occurs or if the problem is recurrent.

18

Pancreatic diseases

The pancreas, through the production of pancreatic secretions, serves vital *exocrine* digestive functions and acts as the site of production of the *endocrine* hormones, insulin and glucagon, controlling glucose homeostasis. Self-digestion by exocrine products is prevented by a carefully balanced suppressor system; disruption of that system by a variety of causes can result in pancreatic inflammation, called pancreatitis. When recurrent, pancreatitis can cause scarring and destruction of pancreatic tissue with resultant loss of exocrine and/or endocrine functions.

Pancreatic anatomy

The pancreas is made up of distinct lobules which are connected by loose areolar tissue that also surrounds the entire gland. Each lobule consists of connective tissue surrounding alveoli, or pouches, that are tubular and almost completely filled with secretory cells. These then join with the ducts of the lobules which drain to the pancreatic duct (Figure 18.1). The islands of connective tissue between the alveoli are termed the islets of Langerhan and contain two types of cells, known as A and B cells, depending on the pattern of staining of the secretory granules they contain; they produce the endocrine secretions of the pancreas involved in glucose homeostasis.

The secretory product of the pancreas, the pancreatic juice, is carried by the pancreatic duct to the duodenum, and there aids digestion, mainly by lipolysis of fats.

The gland has three parts, the right extremity, being broad, is called the *head*, and is connected to the main portion of the organ, or *body*, by a slight constriction, the neck; while its left extremity gradually tapers to form the *tail*. Its length varies from 12.5 to 15 cm, and its weight from 60 to 100 g.

The pancreatic duct commences in the tail where the small duct from the pancreatic lobules join. It runs from left to right through the body, receiving further ducts along the way. Finally it comes into relation with the common bile duct and leaves the head of the gland, passing very obliquely through the mucous and muscular coats of the duodenum, and exiting at the orifice of the papilla of Vater in the descending duodenum. There is often also an additional duct, known as the accessory duct, which is given off from the pancreatic duct in the neck of the pancreas and opens into the duodenum about 2.5 cm above the duodenal papilla.

Embryology

The pancreas develops in two parts. The dorsal part arises as a diverticulum from the dorsal side of the duodenum just proximal to the hepatic diverticulum. This dorsal part forms part of the head, the body and tail. The ventral part develops from a diverticulum that forms from the bile duct and goes on to form the remainder of the head and uncinate process.

At this stage each part has its own duct. The duct of the dorsal part (later known as the accessory

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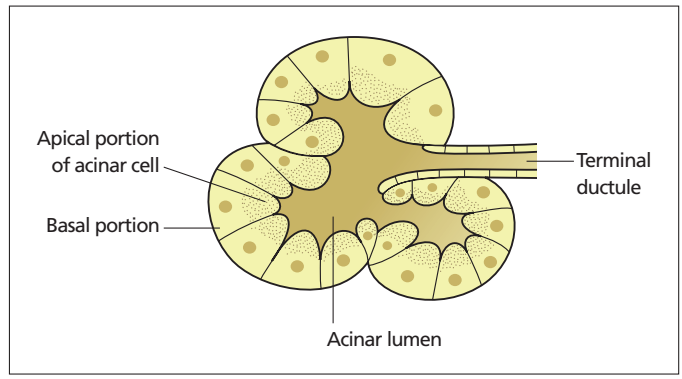

Figure 18.1 Pancreatic acinar structure.

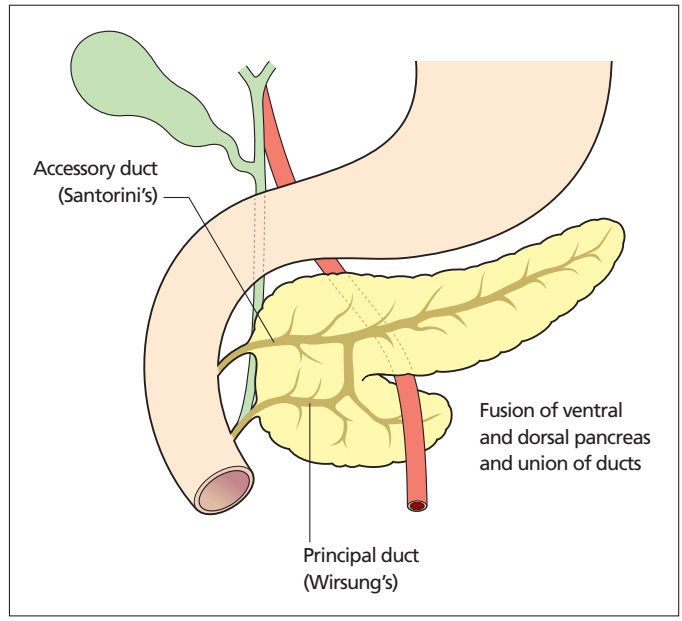

Figure 18.2 Pancreatoduodenal anatomy showing the developing ductal systems.

pancreatic duct) opens independently, while the duct of the ventral part opens with the common bile duct. At about 6 weeks the two parts fuse and form a communication between the two ducts. The pancreatic duct continues to increase in diameter with development whereas the accessory duct remains small and its opening may even be obliterated (Figure 18.2).

While initially the pancreas lies intraperitoneally between the two layers of the dorsal mesogastrium, movement of the stomach draws the dorsal mesogastrium down and to the left. The right surface of the pancreas becomes applied to the posterior abdominal wall, with absorption of the peritoneum covering it, resulting in the posterior aspect of the gland in the adult being devoid of peritoneum and in contact with the aorta, left kidney and its vessels and other retroperitoneal structures.

Physiology

Digestive enzymes

In the acinar cells enzymes are synthesised by the ribosomes of the rough endoplasmic reticulum. These enzymes are then stored, either in active or precursor (pro-enzyme) states within 'zymogen' granules at the apices of the cell. Cholecystokinin (CCK) release in response to a meal results in release of these enzymes and pro-enzymes into the ductules.

The digestive enzymes produced include:

- Amylase for carbohydrates;
- Lipases for fats;
- Proteases for proteins;
- Nucleases for DNA and RNA.

Luminal digestion of carbohydrate, protein and fat reduces them to smaller molecules, which can be absorbed by the intestinal cells, either directly or following digestion by enzymes on the brush border of these cells.

Amylase

Amylases hydrolyses polysaccharides in starch and glycogen to maltose and other small oligosaccharides, which can then be cleaved to glucose by brush border enzymes in the small intestinal mucosa. Salivary glands also produce amylase.

Lipases

The fatty acids of triglycerides in food are hydrolysed off by lipase, producing free fatty acids. This is aided by the conversion of pro-co-lipase from the acinar cells to co-lipase in the small intestine. Co-lipase prevents bile salts from inhibiting the lipolysis of triglycerides.

Prophospholipase A is converted to phospholipase A by trypsin in the small intestine. This then hydrolyses fatty acids from lecithin and phosphatidyl ethanolamine.

Proteases

Trypsin is secreted from the acinar cells as trypsinogen and activated principally in the upper small intestine brush border by an enterokinase. While the pancreas protects itself from its own proteolytic enzymes by secreting them as inactive proenzymes, trypsin may be 'autoactivated' in the acinar cell. Damage by inappropriately activated trypsin is prevented by a trypsin inhibitor that can inhibit activated trypsin and proteases that can cleave trypsin.

Activated trypsin is important as the common activator of other pancreatic enzymes, including more trypsinogen, chymotrypsinogen, proelastase, procarbosypeptidases and prophoshoplipase. Trypsin acts to hydrolyse peptide bonds within the polypeptide chain of proteins.

Nucleotidases

Ribonuclease and deoxyribonuclease digest, respectively, RNA and DNA.

Duct cells and bicarbonate secretion

Pancreatic enzymes require a neutral pH to function. This environment is promoted by the secretion of sodium bicarbonate by pancreatic duct cells to neutralize the gastric acid which enters the duodenum. Pancreatic bicarbonate secretion is stimulated by secretin from endocrine cells in the duodenal mucosa. The normal pancreas secretes about 2 l of pancreatic juice per day, containing 9–18 g of bicarbonate, most of which is reabsorbed by the intestine.

There are two main mechanisms for the production of sodium bicarbonate:

- Pancreatic duct cells use carbonic anhydrase to catalyse the conversion of carbon dioxide and water ($H_2O + CO_2 \rightarrow H_2CO_3^- \rightarrow H^+ + HCO_3^-$);
- An Na^+/HCO_3^- co-transporter located on the basolateral membrane of duct cells can transport sodium into cells followed by transport of HCO_3^- into the duct lumen by a HCO_3^-/Cl^- exchanger.

Chronic pancreatitis

Epidemiology and aetiology

Chronic pancreatitis has a population incidence of 3.5–10 in 100 000 in industrialised countries. In the Western world the major association is with alcohol abuse (80% of cases).

Much rarer factors include:

- Pancreatic duct obstruction (from strictures);
- Metabolic disturbance (hypertriglyceridaemia, hypercalcaemia);
- Genetic mutations:
  - Defects in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene cause pancreatitis in cystic fibrosis but may also play a role in predisposing individuals without cystic fibrosis to chronic pancreatitis;
  - In both tropical pancreatitis and pancreatitis in children, mutations in a serine protease inhibitor gene (*SPINK1*) have been demonstrated in a subgroup of cases: the *SPINK 1* gene product normally inhibits up to 20% of trypsin activity and may predispose to pancreatitis by loss of this mechanism;
  - There is a rare genetic form of chronic pancreatitis closely associated with mutations in the cationic trypsinogen gene: inheritance is autosomal dominant with disease penetrance of about 80%.
- Autoimmunity:
  - A steroid responsive form of chronic pancreatitis has been more clearly characterized and termed autoimmune pancreatitis.

At times no cause can be found and idiopathic chronic pancreatitis is diagnosed, but the incidence of this continues to decrease with improvements in diagnostic techniques.

History

In taking a history it is essential that careful attention is paid to alcohol history. Ancillary history from family members may be necessary. Questions should also be asked about any family history of pancreatitis, personal or family history of autoimmune disorders, use of prescription and illicit drugs, and travel history.

Clinical features

The three major clinical features of chronic pancreatitis are:

- **Pain**: often the major and most difficult to manage clinical problem in chronic pancreatitis. The pain is usually epigastric and may radiate to the back. Because severe pain decreases appetite, it can also contribute to anorexia. Two categories of pain are described: recurrent (type A) pain and continuous (type B) pain. It should be noted that 10–15% of patients never have pain and present with malabsorption.
- **Maldigestion**: recurrent inflammation in chronic pancreatitis may result in so much glandular destruction that the daily endocrine and exocrine requirements of the pancreas cannot be met. In the case of exocrine insufficiency, this usually occurs when lipase and protease secretions decrease below 10% of normal. The resultant malabsorption of carbohydrates, proteins and fats often results in weight loss and steatorrhoea.
- **Diabetes**: pancreatic endocrine insufficiency results in glucose intolerance as insulin production drops below requirements. Polyuria, polydipsia and malaise may occur.

Examination

Examination is often unremarkable. The presence of jaundice should be sought as it might indicate associated biliary disease. Infrequently pseudocysts may be palpable as an abdominal mass. Nutritional assessment is essential as advanced chronic pancreatitis is often associated with malnutrition.

Investigations

Investigations are aimed first at establishing the diagnosis (condition) of pancreatitis and the underlying cause(s), and second at assessing the degree of pancreatic damage (complications).

In particular, the presence of cholelithiasis as a precipitating cause should be sought and treated, and the diagnosis of autoimmune pancreatitis should be considered because of the responsiveness of this condition to steroid therapy. Finally, patients with chronic pancreatitis are at increased risk of pancreatic cancer, particularly with increasing age and in smokers, and these groups of patient should be considered for surveillance for the development of pancreatic lesions.

Diagnosis can be difficult because amylase and lipase levels are frequently normal. Diagnosis then relies on the detection of structural changes and, late in the disease, exocrine and endocrine abnormalities. Initial blood tests (taken in the convalescent phase, as episodes of acute pancreatitis may falsely alter blood chemistry) should look for hypertriglyceridaemia and hypercalcaemia as well as evidence of biliary obstruction by measuring bilirubin, ALP and GGT. Late

in the disease, endocrine dysfunction should be tested for by fasting glucose and glucose tolerance testing if indicated. Exocrine function is most commonly tested for using faecal elastase, reduced levels indicating reduced exocrine function.

Radiological investigation should include ultrasound of the abdomen wherever biliary disease might be suspected. CT provides the best means of assessing the degree of calcification of the pancreas. MRCP provides information about the pancreatic parenchyma and ductal system as well as the biliary tree. ERCP is reserved for cases in which the above investigations cannot convincingly rule out cholelithiasis or where the pattern of radiological change suggests that there may be isolated main pancreatic duct stones, the endoscopic removal of which might benefit the patient. Finally, obtaining tissue from pancreatic masses is increasingly important in differentiating between benign and malignant lesions and, as well as open surgical and laparoscopic biopsy, endoscopic ultrasound and fine needle aspiration are increasingly being used.

Management

Treatment is largely symptomatic and aimed at managing pain, and exocrine and endocrine insufficiency, as well as nutritional support. The most important factor overall is the abstinence from alcohol and smoking in alcoholic pancreatitis. Other precipitating factors should be sought and corrected, such as anatomical abnormalities or metabolic disease. Surgery and other interventional procedures are mostly reserved for the treatment of underlying anatomical causes or complications of chronic pancreatitis.

Pain management

Pain compromises quality of life in chronic pancreatitis and is of primary concern. Use of analgesia should always start with a conventional analgesic, including paracetamol, but often opiates are required. When prescribing opiates the prominent side-effects of CNS depression, alterations of GI motility and induction of dependence must be kept in mind.

Other strategies of pain relief are used but remain unproven, including inhibition of pancreatic enzyme secretion using pancreatic enzyme therapy and the use of antioxidants, coeliac plexus block, endoscopic procedures and surgical drainage and resection.

Exocrine insufficiency

Steatorrhoea is defined as faecal fat >7 g/day. However, in practice, faecal fat measurement is rarely used and the decision to treat with pancreatic enzymes is based on nutritional status and subjective reports of steatorrhoea. The aim of treatment is to treat the steatorrhoea and correct the nutritional consequences of fat malabsorption, but a significant increase in body weight is rarely achieved. Generally a dose of 25000–50000 U lipase/meal is recommended, but a higher dose or combination with a proton pump inhibitor may be required.

Diabetes

Treatment is no different from patients with type 1 diabetes, but it must be recalled that the coexisting deficiency of glucagon puts chronic pancreatitis patients at increased risk of hypoglycaemia. This is particularly true when compliance is poor and/or there is continued alcohol consumption or autonomic neuropathy. Given that the survival of such patients is limited, the aim should be adequate control of glucose and avoidance of hypoglycaemia. Aggressive glucose management should be reserved for patients with good compliance and cessation of alcohol.

Nutrition

There is no specific diet known to be beneficial in chronic pancreatitis but abstinence from alcohol and the intake of smaller but more frequent meals is recommended. Fat restriction is not recommended and steatorrhoea should instead be treated with pancreatic supplements. Fat-soluble vitamin deficiencies occur particularly with ongoing alcohol use and should be screened for and treated.

Pancreatic tumours

Pancreatic carcinoma

The majority of pancreatic cancers are adenocarcinomas that arise from ductal and acinar cells. They are twice as common in men compared to women and occur at a mean age of 55 years. Risk factors for pancreatic carcinoma include smoking and chronic pancreatitis.

Clinical features

At initial presentation the majority of patients have advanced disease:

- Most patients have severe abdominal pain often radiating to the back;
- Weight loss is common;
- Obstructive jaundice is a frequent result of lesions in the head of the pancreas;
- Cancer in the body and tail may cause splenic vein obstruction with resultant splenomegaly, gastric and oesophageal varices, and GI haemorrhage;
- Glandular destruction by the tumour may lead to diabetes and/or pancreatic exocrine insufficiency.

Investigations

- Laboratory tests show elevated ALP and bilirubin in bile duct obstruction. Ca 19-9 is not useful in diagnosis but, if positive, may be used to monitor response to treatment.
- Helical CT or MRCP are the preferred tests.
- In the case of obstructive jaundice, it is reasonable to use ERCP as the initial investigation.
- Fine needle aspiration is usually required for confirmation of the diagnosis, using CT or endoscopic ultrasound guidance.

Management

The overall survival rate for pancreatic cancer is <6%, making it the worst of all the solid organ cancers. The only chance for cure is complete resection of the tumour. However, only 30% of patients with tumours in the head of the pancreas, and only 10% of those with cancer in the body and tail, can be offered curative resection at presentation. Adjuvant chemotherapy and radiation therapy are commonly used.

Given the majority of patients have incurable disease, symptomatic management is of the utmost importance. Moderate to severe pain should be treated with oral opioid analgesics at sufficient dose. Concerns about addiction should not prevent this. In difficult to control pain, percutaneous or operative splanchnic (coeliac) block may be used. Pruritis is best treated by relieving obstruction with palliative surgery or endoscoping biliary stenting. Where this is not possible, cholestyramine or phenobarbitol may be of some benefit. Pancreatic insufficiency is treated with pancreatic supplements.

Cystadenocarcinoma

This rare adenomatous tumour results from malignant degeneration of a mucous cystadenoma. Patients present with upper abdominal pain and a palpable mass. CT or MRI demonstrate a cystic mass that contains debris. The tumour is slow growing and slow to metastasise, and prognosis following surgical excision is good.

Intraductal papillary-mucinous tumour

This rare tumour most commonly occurs in women, in the tail of the pancreas. The tumour over-secretes mucin, causing pain and recurrent bouts of pancreatitis. Disease may range from benign to malignant and cannot be differentiated without surgical removal. Initial diagnosis is made by CT, MRCP or ERCP. ERCP may show the typical 'fish eye' appearance, where the duodenal papilla is seen to be gaping with 'shiny' mucus bulging through the terminal duct. Following surgical resection, prognosis is excellent for benign disease. Malignant disease has a 5-year survival of 50–75%.

Pancreatic endocrine tumours

These rare tumours arise from the islet and gastrin-producing cells of the pancreas. They may be non-functioning and present with biliary obstruction, bleeding or abdominal masses; or functioning (hormone secreting) and present with an endocrine syndrome, depending on the hormone produced.

19

Biliary diseases

The biliary system is concerned with the transport of bile, including timely release and *en route* concentration, from the liver into the duodenum. Disruption of the flow of bile has consequences in the form of pain, inflammation, colonisation by micro-organisms and infection, as well as in terms of loss of essential digestive functions of bile. Disruption of bile flow most commonly occurs because of mechanical blockage caused by biliary stones. However, other acquired and congenital causes also contribute.

Embryology

The liver arises as a hollow outgrowth from the portion of the gut which goes on to become the descending part of the duodenum. This diverticulum gives off two buds of cells which become the right and left lobes of the liver. The original diverticulum from the duodenum forms the common bile duct, and from this the cystic duct and gallbladder arise as a solid outgrowth which later acquires a lumen (Figure 19.1).

Biliary anatomy

The bile ducts arise as tiny passages in the liver cells which communicate with the **intercellular biliary passages** (bile capillaries or cannaliculi). These passages radiate to the circumference of the lobule, and open into the interlobular bile ducts, accompanying the portal vein and hepatic artery.

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They then join with other ducts to form two main trunks, which leave the liver at the porta hepatis and join to form the **hepatic duct**.

The large biliary ducts have an external or fibrous and an internal or mucous layer. The mucous coat is continuous with the lining membrane of the hepatic ducts and gallbladder, and also with that of the duodenum. The mucous membrane is a columnar epithelium, with numerous mucous glands. About 4 cm after the union of the two main trunks to form the hepatic duct, it is joined at an acute angle by the cystic duct, and so forms the common bile duct. The hepatic duct is accompanied by the hepatic artery and portal vein.

The gallbladder is divided into a fundus, body and neck, and consists of three coats: an external serous coat derived from the peritoneum, a fibromuscular coat which forms the framework of the sac and an internal mucus which is elevated into minute rugae. Opposite the neck of the gallbladder, the mucous membrane projects inward in the form of oblique ridges or folds, forming a sort of spiral valve.

The **cystic duct**, which is about 4 cm long, has a mucous lining that is thrown into a series of crescentic folds, from 5 to 12 in number, similar to those found in the neck of the gallbladder. They form a continuous spiral valve, which, when the duct is distended, results in dilatation of the spaces between the fold, so as to give the cystic duct a twisted appearance.

The **common bile duct**, formed by the junction of the cystic and hepatic ducts, is about 7.5 cm long and <7 mm in diameter (this may increase with age: approximately 1 mm each decade above the age of 50 years). Near its distal end, it lies alongside the terminal part of the pancreatic duct. The two ducts unite and share an opening at the tip of the duodenal papilla. The short tube formed

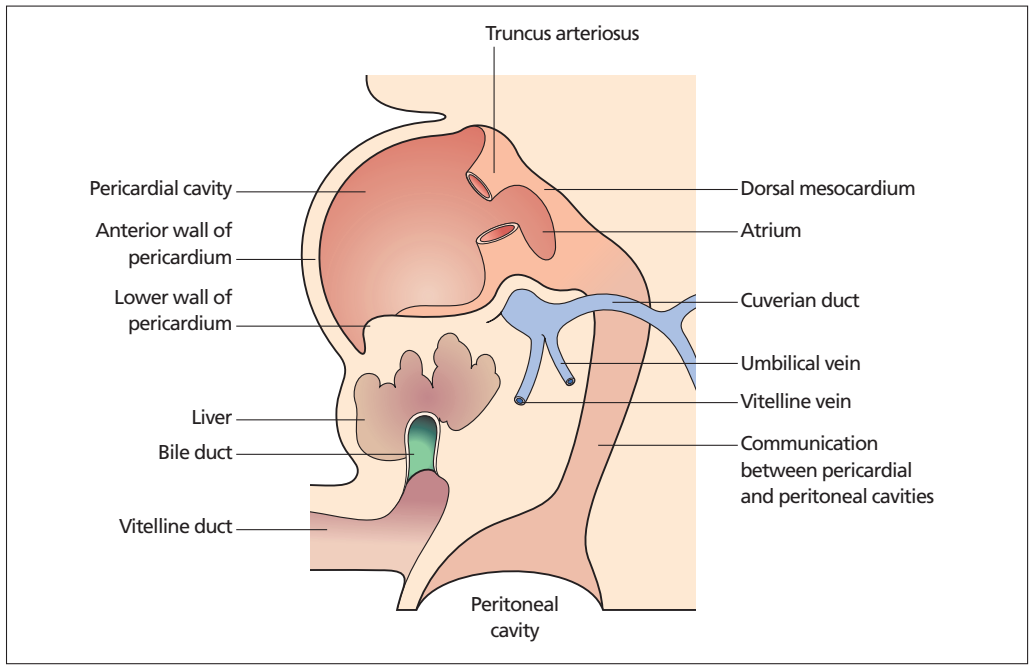

Figure 19.1 Human embryo at 3-mm length stage, showing developmental structures of the biliary tree.

by the union of the two ducts is dilated into the **ampulla of Vater**.

Biliary physiology

Over a 24-h period, a normal adult human produces 400–1100 ml of hepatic bile. Bile is composed of:

- Water (the primary component);
- Electrolytes;
- Bile salts, synonymous with bile acids (they induce influx of water and electrolytes in the canaliculi by active transport and passive diffusion);
- Bilirubin (from degradation of haem compounds from degenerative red blood cells);
- Phospholipids and cholesterol;
- Proteins that regulate GI function;
- Drugs and drug metabolites (including potentially toxic compounds).

From the cannaliculi bile passes into the interlobular ducts, then the common hepatic duct. About 50% of the bile secreted while fasting is collected in the gallbladder. The gallbladder then absorbs up to 90% of the water, concentrating and storing bile. Eating results in the release of gut hormones and cholinergic stimulation. These initiate gallbladder contraction and biliary sphincter relaxation, promoting the passage of bile from the gallbladder into the duodenum. The concentrated bile thus released solubilises intestinal fats and fat-soluble vitamins, facilitating their absorption. During fasting an increase in sphincter tone facilitates gallbladder filling.

The proximal small intestine allows limited passive diffusion of bile salts such that 90% of bile salts reach the terminal ileum. Here there is active absorption of bile salts into the portal venous circulation. Bile salts are thus returned to the liver and circulate through this pathway – the enterohepatic circulation – 10–12 times/day.

Biliary microbiology

Biliary infection occurs often in association with cholelithiasis. It can take acute and chronic forms and predominately involves the gallbladder

Table 19.1 Characteristics of different gallstone types.

Characteristic	Cholesterol	Black pigment	Brown pigment
Composition	Cholesterol with calcium bilirubinates	Black pigment polymer with calcium bilirubinates and phosphates	Calcium bilirubinates with cholesterol and calcium palmitate
Colour	Yellow–white	Black to dark brown	Yellow to orange
Shape and texture	Hard and shiny, round or faceted	Shiny or dull, faceted	Soft and greasy, ovoid
Number	Single or multiple	Multiple and numerous	Single or multiple
Location	Usually gallbladder	Usually gallbladder	Usually bile ducts
Associations	Female gender, multiparity Diabetes Oral contraceptives Obesity or rapid weight loss Family history	Haemolysis Cirrhosis Crohn's disease Total parenteral nutrition	Structural biliary disease (strictures, sclerosing cholangitis, surgery)
Cause	Increased cholesterol with or without decreased bile salt excretion	Increased bilirubin and calcium excretion into bile Increased bile pH	Bacterial infection causes hydrolysis of bilirubin conjugates

(cholecystitis) or the bile ducts (cholangitis), discussed separately below.

The organisms involved are generally intestinal commensals:

- Commonest are Gram negatives (e.g. *Escherichia coli*, *Klebsiella*, *Enterobacter*);
- Less common are Gram positives (e.g. *Enterococcus* spp.) and mixed anaerobes (e.g. *Bacteroides*, *Clostridia*).

Cholelithiasis

Cholelithiasis, or the presence of gallstones, is common. However, the majority of patients (60–80%) do not develop symptoms associated with gallstones. Management centres on population measures to reduce rates of gallstone formation and, in the individual patient, stratification as to the risk of symptoms and complications in those with asymptomatic, incidentally discovered gallstones. Generally patients with symptomatic gallstones should have cholecystectomy if tolerated.

Gallstone formation

Gallstones are made up of poorly soluble components of bile precipitated on a three-dimensional matrix of mucins and proteins. The three main types of gallstones are cholesterol stones, black pigment stones and brown pigment stones (Table 19.1). For gallstone formation to occur there must be:

- Supersaturation;
- Excess of promotors over inhibitors of crystallization;
- A matrix template on which crystallization can occur;
- Bile stasis (retention in the gallbladder to allow time to grow).

The major precipitates are cholesterol, calcium bilirubinates and calcium salts of phosphate, carbonate and palmitate.

The vast majority of gallstones in Western countries are cholesterol or mixed type. It is interesting to note that while pigment gallstones predominate in Asian countries, Asians who take up a Western diet become more prone to cholesterol stones.

Normally, in the gallbladder, bile is concentrated by active absorption of water and electrolytes. Phospholipids and biliary cholesterol are absorbed so that the concentration of cholesterol relative to bile salts is actually lower than in hepatic bile. Supersaturation with cholesterol therefore can occur only if the bile secreted by hepatocytes is already supersaturated and/or the composition or pH of bile is altered in the extrahepatic bile ducts or gallbladder.

When there is supersaturation, if a suitable matrix is present, the minerals crystallize on a matrix template to form a miniature calculus or nidus. The matrix is made up of proteins and glycoproteins. For this nidus to then grow to form a gallstone, there needs to be bile stasis due to impairment of emptying of the gallbladder or bile flow in the ducts.

Epidemiology and public health measures

Risk factors for cholesterol gallstones include:

- Demographic factors:
  - Family history;
  - Older age;
  - Female gender;
  - Pregnancy and multiparity.
- Abnormal eating behaviours:
  - Obesity;
  - Rapid weight loss;
  - Prolonged fasting.
- Systemic diseases:
  - Diabetes mellitus;
  - Crohn's disease;
  - Spinal cord injury.
- Iatrogenic causes:
  - Somatostatin(-analogue) treatment;
  - Sex hormone treatment;
  - Total parenteral nutrition.

Possible *preventative factors* include:

- High fibre diet;
- Low consumption of saturated fatty acids;
- High relative amounts of cis- *versus trans*-fatty acids;
- Nut consumption;
- Moderate physical activity.

Clinical features

- Pain: Typically right hypochondrial or epigastric;
- Radiates to the upper back or right shoulder;
- Steady and intense, occurs more than an hour after meals (especially fried or fatty foods);
- Often associated with an urge to walk (75% of patients);
- Each episode lasts 1–24 h;
- More likely to be gallstone related when there is no associated heartburn and no relief with bowel movements.
- Murphy's sign (deep inspiration exacerbates the pain during palpation of the right upper quadrant (RUQ) and halts inspiration) develops with involuntary guarding of right-sided abdominal muscles.
- Fever (common): usually low grade.
- In the elderly, fever may not develop, and the first or only symptoms may be systemic and non-specific (e.g. anorexia, vomiting, malaise, weakness).

Investigations

- **Routine tests:** because only 10% of gallstones are calcified, plain abdominal X-ray is infrequently helpful. In addition, given the intermittent nature of symptoms, nor are routine blood tests, although repeated liver tests timed to the onset of pain may give extra clues as to the cause of pain.
- **Advanced tests:** magnetic resonance cholangiopancreatography (MRCP) has high specificity and sensitivity in choledocholithiasis, giving it an accuracy very similar to ERCP. However, it has limitations in the detection of small gallstones (<4 mm) and gallstones that sit close to the ampulla of Vater. Endoscopic ultrasonography (EUS) has proven useful in detecting very small gallstones (<3 mm) and may be needed if other studies are equivocal.

Risk stratification of patients with asymptomatic gallstones

The average risk of someone with gallstones developing symptomatic gallstones is low at approximately 2.0% per year, the yearly incidence of complications is 0.3% and the risk for gallbladder cancer is 0.02%. Hence most patients need no therapy. However, the subgroup with high risk of symptoms and/or gallbladder cancer, will generally benefit from prophylactic cholecystectomy.

Indications for cholecystectomy:

- Gallbladder polyps which are rapidly growing or that are >1 cm;
- 'Porcelain gallbladder', a radiological sign;
- Solitary stone or total stone burden >3 cm;
- Sickle cell anaemia;
- Morbidly obese patients undergoing bariatric surgery.

Primary prevention of gallstones in high-risk groups

High-risk groups can benefit from modulation of therapy to avoid gallstones:

- During weight loss:
  - Limitation of weight loss to a maximum rate of 1.5 kg/week;
  - Addition of 10 g of fat to a low-calorie diet;
  - Evidence for NSAIDs is contradictory;
  - Ursodeoxycholic acid (UDCA) is efficacious and cost beneficial.
- Daily intravenous cholecystokinin or amino acids during total parenteral nutrition.
- UDCA during somatostatin analogue therapy.

Management of symptomatic gallstones

Cholecystectomy

After symptoms develop, the risk of recurrent symptoms decreases with time:

- Within 1 year from the first pain attack about 50% have a second attack;
- About 30% of patients will have only one pain attack;
- After 5 years symptom free, the risk returns to that of asymptomatic patients.

Symptomatic patients are at higher risk of complications (i.e. acute cholecystitis, acute pancreatitis, cholangitis); the risk is about 1–2%, as compared to 0.1–0.2% in asymptomatic patients. Open cholecystectomy, previously the treatment of choice, is safe and effective with an overall mortality of 0.1–0.5%. However, laparoscopic cholecystectomy has become the treatment of choice because it is associated with shorter convalescence, decreased post-operative discomfort, improved cosmetic results and no increase in morbidity or mortality. In about 5% of cases the procedure must be converted to an open one.

Non-surgical alternatives

Where surgery is declined or surgical risks are high, UDCA can sometimes dissolve gallbladder stones:

- Treatment given for many months;
- Must be cholesterol stones;
- Stones cannot be too large (<1.5 cm);
- Gallbladder should be free of obstruction.

However after UDCA, stones recur in about half of patients by 5 years, and it is not successful when used in patients with highly symptomatic gallstones.

ERCP and sphincterotomy may be sufficient treatment for patients with gallstones who are not suitable for surgery.

Acute cholangitis

Aetiology

Acute bacterial cholangitis develops when bacterial infection complicates obstruction within the biliary tract. Partial obstruction imparts increased risk compared to complete obstruction. Infection is generally thought to occur through direct extension of bacteria from the duodenum. Haematogenous spread through the portal venous system could be another route. Bacterial colonisation of the bile duct alone generally does *not* result in cholangitis.

Causes of acute bacterial cholangitis:

- Choledocholithiasis or sludge;
- Biliary strictures;
- Choledochal cysts, choledochocele, Caroli's disease;
- Stenosis of the papilla of Vater;
- Parasitic infections;
- Iatrogenic (e.g. post-ERCP).

Clinical features

The classical presentation is with Charcot's triad:

- Fever;
- RUQ pain (may be absent in the elderly);
- Jaundice.

In severe cases, mental confusion and hypotension may also be present (Reynold's pentad). In these cases, urgent biliary decompression is needed.

Investigations

- **Bloods**: all patients should have serum biochemistry, FBC and a clotting screen performed. In the early stage there may be a pronounced and disproportionate increase of aminotransferases (ALT, AST). This may cause confusion with viral hepatitis, since in the early

stage bile ducts are often not (yet) dilated on ultrasound.

- **Transabdominal ultrasound** is the first step in detecting bile-duct (as well as associated gallbladder) stones. However, the distal bile duct may be difficult to visualise because of air-containing intestinal loops in front of it. Whilst the specificity of ultrasound in stone detection is almost 100%, the sensitivity in detecting bile-duct stones is rather low (27–49%). The finding of bile-duct dilatation is invaluable as it indicates the presence of post-hepatic obstruction.
- **MRCP** is more sensitive than transabdominal ultrasound (overall > 90%) in detecting bile-duct stones. However, its sensitivity is lower in cases with small stones and/or very dilated bile ducts.
- **Endoscopic ultrasonography** allows excellent visualisation of the bile duct, including the distal part that may be difficult to see on conventional ultrasound. It has a high sensitivity to detect bile-duct stones.
- **ERCP** is considered the gold standard investigation. The disadvantages are its invasiveness and risk of complications (morbidity 3%, mortality 0.2% for diagnostic ERCP). A great advantage is the possibility of proceeding to therapeutic ERCP with papillotomy, stone extraction and/or nasobiliary drainage or stenting.

Differential diagnosis:

- Gallbladder:
  - Acute cholecystitis;
  - Mirizzi's syndrome.
- Intra-abdominal:
  - Acute appendicitis;
  - Perforated duodenal ulcer;
  - Hepatic abscess;
  - Acute hepatitis.

Management

While 80–90% of cholangitis patients respond satisfactorily to initial conservative therapy with broad-spectrum antibiotics and adequate intravenous hydration, it is wise to perform ERCP in all patients as early as possible: immediately in septic patients, otherwise within 24 h.

Choice of antibiotics is influenced by patient characteristics (e.g. antibiotic hypersensitivity, renal function, hearing loss, severity of disease, previous instrumentation of the bile ducts), and results of biliary (if taken) and blood cultures.

Endoscopic therapy for acute gallstone cholangitis is superior to surgical treatment. Percutaneous transhepatic drainage or surgery should be considered when ERCP is impossible or has failed in expert hands. If there is significant coagulation disturbances, large and multiple stones or an unstable patient, nasobiliary drain placement or biliary stents are preferred as initial treatment. Stone removal can then be performed at a later stage, after recovery from the acute episode. Elective cholecystectomy should be performed in the majority of cases.

Cholecystitis

Aetiology

Cholecystitis is caused by obstruction of the cystic duct usually by a gallstone, leading to distension and subsequent chemical or bacterial inflammation of the gallbladder. 95% of people with acute cholecystitis have gallstones (**calculous cholecystitis**) and 5% lack gallstones (**acalculous cholecystitis**). Positive cultures of the bile or gallbladder wall are found in 50–75% of cases of acute cholecystitis. The cause of acalculous cholecystitis is uncertain and may be multifactorial.

Epidemiology

Of those admitted to hospital for biliary tract disease, 20% have acute cholecystitis, and the number of cholecystectomies carried out is steadily increasing, especially in elderly people. Acute calculous cholecystitis is three times more common in women up to the age of 50 years and about 1.5 times more common in women thereafter.

Clinical features

Patients present with unremitting RUQ pain, anorexia, nausea, vomiting and fever. Severe acute cholecystitis can lead to necrosis of the gallbladder wall, known as **gangrenous cholecystitis**. The complications of cholecystitis include perforation of the gallbladder, pericholecystic abscess and fistula.

Box 19.1 Comparing laparoscopic *versus* open cholecystectomy.

- Reduces hospital stay, duration of surgery and intra- and post-operative complications
- Conversion from laparoscopic to open cholecystectomy is necessary in 4–27% of cases
- Laparoscopic cholecystectomy carries a higher incidence of bile duct injury

Management

The treatment of choice for cholecystitis is open or laparoscopic cholecystectomy (Box 19.1) undertaken *early* (within 7 days of onset of symptoms) rather than *delayed* (≥6 weeks after onset of symptoms) as it reduces the duration of hospital stay.

Observation alone has a failure rate after 8 years of 30%, but there is no difference in the rate of gallstone-related complications (recurrent cholecystitis, pancreatitis, intractable pain) or emergency admissions for pain. For this reason those with acute cholecystitis who have multiple comorbid conditions and relative contraindications for cholecystectomy may be treated with antibiotics, a low-fat diet and, in some instances, a cholecystostomy tube. If the comorbidity becomes better controlled, delayed cholecystectomy is appropriate.

Acalculous biliary pain

Recurrent biliary-type abdominal pain in patients with no evidence of cholelithiasis is a perplexing clinical dilemma, and evaluation and treatment of these patients is controversial. The frequency of biliary-type pain without gallstones in the population may be as high as 7% in men and 20% in women. Synonyms for the term acalculous biliary pain include: gallbladder dysfunction, functional gallbladder and sphincter of Oddi dysfunction (SOD), gallbladder dyskinesia, biliary dyskinesia, chronic acalculous cholecystitis and chronic acalculous gallbladder disease.

Aetiopathophysiology

This remains incompletely understood:

Box 19.2 Classification of sphincter of Oddi.

Type 1
- Biliary pain
- Abnormal liver enzyme levels
- Fixed sphincter of Oddi stenosis on radiograph

Type 2
- Biliary pain and transient elevation of enzyme level and/or
- Dilated bile duct and/or
- Delay in emptying of bile duct

Type 3
- Biliary pain only

- Altered gallbladder motility is the most commonly accepted abnormality;
- Impairment of gallbladder filling;
- Gallbladder hyperalgesia.

Functional disorders of adjacent structures, classically SOD (Box 19.2), have been implicated in the pathogenesis of recurrent epigastric or RUQ abdominal pain following cholecystectomy. That SOD might exist in patients with an intact gallbladder has been suggested but remains controversial.

Clinical features

The clinical features of this pain are summarised in Box 19.3.

Investigations

Gallstone disease and structural abnormalities must be excluded before the diagnosis of a functional disorder can be considered.

- Cholecystokinin cholescintigraphy to measure the gallbladder ejection fraction (GEF) has been advocated as a way to select patients with acalculous biliary pain who would benefit from cholecystectomy.
- ERCP with sphincter of Oddi manometry (SOM) has been used to identify patients who might respond to biliary endoscopic sphincterotomy (ES). It must be noted that SOD increases the risk for post-ES pancreatitis, occurring in as many as 22% of patients.

Box 19.3 Diagnostic criteria for gallbladder and sphincter of Oddi disorders.

Must include episodes of pain located in the epigastrium and/or right upper quadrant and all of the following:

- Episodes lasting 30 min or longer
- Recurrent symptoms occurring at different intervals (not daily)
- Pain builds up to a steady level
- Pain severe enough to interrupt patient's daily activities or lead to an emergency department visit
- Pain not relieved by bowel movements
- Pain not relieved by postural change
- Pain not relieved by antacids
- Exclusion of other structural disease that would explain the symptoms

Supportive criteria

The pain may present with one or more of the following:

- Pain associated with nausea and vomiting
- Pain radiates to back and/or right infrasubscapular region
- Pain awakens patient from sleep in the middle of the night

Management

Given the risks of cholecystectomy and SOM, and the lack of clear evidence of benefit in the majority of patients, a conservative approach is advocated. Careful evaluation of psychological issues is essential, and treatments targeting chronic visceral pain (such as tricyclic antidepressants) should be considered.

Structural bile duct abnormalities

The three major adult manifestations of cholestasis are primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and cholangiocarcinoma. Drug-related and congenital biliary abnormalities are discussed in Chapters 23 and 25, respectively.

Primary sclerosing cholangitis

PSC has a male predominance, typically affecting young men around age 40 years. There is a strong association with inflammatory bowel disease (IBD), especially ulcerative colitis. The estimated prevalence is 6 in 100 000. PSC is an idiopathic, chronic, progressive liver disease that causes inflammation, fibrosis and strictures in the intrahepatic and extrahepatic bile ducts.

Clinical features

These include jaundice, steatorrhoea, pruritus, weight loss and failure of proper absorption of calcium and fat-soluble vitamins. However, many patients have no symptoms or vague symptoms of fatigue and upper abdominal pain. Examination may reveal xanthomas of the eyes, neck, chest, back and extensor surfaces.

Investigations

Laboratory tests show elevated conjugated bilirubin, an ALP that is often more than three times the upper limit of normal and an elevated GGT.

Management

This primarily involves symptom management. Liver transplantation is the only life-extending therapy. Surveillance for cholangiocarcinoma is warranted; however, there is no consensus as to how this should be conducted. Patients with PSC complicating IBD require more frequent colonic surveillance than those with IBD alone because of an increased risk of colon cancer.

Primary biliary cirrhosis

PBC is an autoimmune cholestatic liver disease in which the epithelial cells lining the intrahepatic bile ducts are damaged by the immune system. It predominately affects women aged 30–65 years but can occur in those as young as their late teens. The male-to-female ratio is 1 : 10.

Clinical features

These typically include fatigue, intense pruritus, cutaneous hyperpigmentation, xanthelasmas and hepatosplenomegaly. The rate of progression is slow. PBC is often associated with various autoim-

mune diseases, such as scleroderma, thyroiditis and Sjögren's syndrome.

Management

UDCA is the first-line treatment early in disease and can slow its progression, but is less effective later in disease. Liver transplant is the only treatment that prolongs life in PBC.

Cholangiocarcinoma

Cholangiocarcinoma is a slow-growing malignancy of the bile duct. It is the second most common primary hepatic tumour (after hepatoma). Groups at high-risk include:

- Parasitic diseases of the biliary tract (*Clonorchis sinensis* or *Opisthorchis viverrini*);
- Congenital choledochal cysts;
- IBD (10-fold increased risk);
- PSC (10% of cases);
- History of other malignancy (10% of cases);
- Previous surgery for choledochal cyst or biliary atresia;
- Alpha-1-antitrypsin deficiency;
- Autosomal dominant polycystic kidney disease;
- Gallstones (20–50% of cases, probably coincidental);
- Papillomatosis of the bile ducts;
- Thorotrast exposure;
- Chronic typhoid carrier status.

Clinical features

Intrahepatic tumours may cause abdominal pain, palpable masses and weight loss, with progressive obstructive jaundice in 90%. Painless jaundice occurs in 12%. Advanced disease may be complicated by cholangitis or acute cholecystitis, or anaemia (due to chronic blood loss secondary to papillary tumours). Physical examination may demonstrate hepatomegaly and a palpable mass in 18% of patients (the gallbladder may be palpable with distal tumours).

Investigations

Tumours, which may be nodular or diffuse, are classified as:

- Intrahepatic (10% of cases);
- Extrahepatic (25% of cases);
- Perihilar bile duct tumours (65% of cases). If they involve the bifurcation of the hepatic duct, they are known as Klatskin's tumours.

The modality most likely to show tumour depends on the type of tumour:

- Ultrasonography is the first-line investigation;
- Abdominal CT may demonstrate the tumour if the malignancy is nodular and mass-like;
- MRCP demonstrates stricture-causing tumours but does not allow distension of the duct and may not detect long segments and minimal narrowing in diffuse sclerosing tumours;
- ERCP is a more definitive investigation that can depict the periampullary tumour.

Management

- **Complete surgical resection** is the only therapy to afford a chance of cure:
  - <20% of intrahepatic tumours are resectable, and 5-year survival rate in those undergoing resection is 5–15%;
  - Resection is more often possible in patients with mid-ductal (33%) or distal tumours (56%), with a 5-year survival rate of 39%.
- **Palliation**:
  - ERCP drainage with or without endoluminal stenting is preferred;
  - Percutaneous radiological drainage may be needed for proximal lesions;
  - Chemotherapy (often as a radiosensitising agent, before palliative radiotherapy);
  - Surgical bypass can also be used for palliation (but most patients die within a year of diagnosis).
- **Orthotopic liver transplantation** is considered for some patients with proximal tumours who are not candidates for resection because of the extent of tumour spread in the liver. However, its use is controversial, primarily because cholangiocarcinoma almost invariably recurs in the transplanted liver.

20

Chronic liver disorders

Chronic liver disease results from hepatocellular injury and necrosis, often with a degree of underlying fibrosis of the liver. Symptoms may be a result of loss of the:

- Detoxifying function of the liver (jaundice, hepatic encephalopathy);
- Synthetic function of the liver (hypoalbuminaemia, clotting factor deficiencies);
- Portal hypertension (oesophageal and other varices, hypersplenism, ascites);
- Complications of the above (GI bleeding, spontaneous bacterial peritonitis).

Jaundice

Jaundice results when the liver's capacity to convert and excrete bilirubin as bile is exceeded. This can result from:

- Over production of bilirubin;
- Reduction in the eliminatory capacity of the liver.

Bilirubin is the breakdown product of haem (from haemoglobin and other haemoproteins). It is bound to albumin in the plasma, but at the hepatocyte membrane it dissociates and enters the hepatocyte. It is then conjugated, primarily with glucuronic acid, and excreted as bile.

Thus jaundice can be divided into three main mechanisms (Table 20.1):

- **Prehepatic**: increased degradation of haem (due to haemolysis) leading to haem concentrations that cannot be cleared by the normal conjugative mechanisms, resulting in a predominately unconjugated hyperbilirubinaemia;
- **Hepatic**: liver damage and/or inflammation affecting the conjugative and excretory ability of the liver so that the normal bilirubin load cannot be excreted, resulting in a predominately unconjugated, or mixed conjugated and unconjugated hyperbilirubinaemia;
- **Posthepatic**: obstruction of the biliary outflow tract at any level, leading to an inability to excrete conjugated bilirubin in bile, resulting in a conjugated hyperbilirubinaemia.

Unconjugated bilirubin is water insoluble and thus is not excreted in urine. Conjugated bilirubin excreted in bile is converted to urobilinogen in the terminal ileum and then reabsorbed as part of the enterohepatic circulation before being excreted in urine. That which is not reabsorbed is further converted to urobilin, then stercobilin, giving faeces its normal colour. Testing for the different by-products of haem excretion in the blood and urine and observation of the stool give clues as to the cause of jaundice. Obstruction of the biliary system results in pale stools (decreased stercobilin) and dark urine (increased conjugated bilirubin, which is unable to be excreted into bile, but no urobilinogen).

Portal hypertension

Raised pressure in the portal venous system is generally a result of increased resistance classified as occurring within the sinusoids (sinusoidal), proximal to the hepatic sinusoids or distal to the sinusoids (pre- or post-sinusoidal respectively).

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Table 20.1 Classification of jaundice by cause, symptoms and investigation features.

Type of jaundice	Laboratory features	Clinical features	Common causes
Pre-hepatic (haemolytic)	Blood: unconjugated hyperbilirubinaemia Urine: no bilirubin present, urobilinogen increased	Jaundice Normal urine Normal stool	Haemolysis Kidney diseases (e.g. haemolytic uraemic syndrome) Diseases with increased rate of haemolysis (e.g. sickle cell anaemia, glucose-6-phosphate dehydrogenase deficiency, malaria)
Hepatic	Blood: hyperbilirubinaemia unconjugated or mixed conjugated and unconjugated Urine: bilirubin present, urobilinogen may be increased but variable	Jaundice Urine dark Normal stool	Commonest: acute hepatitis, alcoholic liver disease, drug hepatotoxicity Less common causes: primary biliary cirrhosis, Gilbert's syndrome (a genetic disorder of bilirubin metabolism present in 5% of the population, which can result in mild jaundice), metastatic carcinoma
Posthepatic (obstructive/ cholestatic)	Blood: conjugated hyperbilirubinaemia Urine: increased conjugated bilirubin, no urinary urobilinogen	Jaundice Severe itching Urine dark Stools pale	Extrahepatic biliary disease (most commonly, gallstones in the common bile duct and cancer in the head of the pancreas; rarer, strictures of the common bile duct, biliary atresia, ductal carcinoma, pancreatitis and pancreatic pseudocysts, liver flukes in the common bile duct) Intrahepatic cholestasis

Another classification system divides the cause into hepatic, pre- and post-hepatic.

The portal system is formed by the confluence of the splenic and superior mesenteric veins. The critical physiological measure is the 'portal pressure gradient' (the difference in pressure between the portal vein and hepatic veins), and portal hypertension is defined as this gradient reaching 12 mmHg or greater. Increased pressure in the portal system results in:

- Collateral vessel formation (in particular varices);
- Ascites;
- Increased risk of hepatorenal syndrome;
- Hepatic encephalophathy;
- Splenomegaly (enlargement of the spleen) with consequent sequestration therein of red blood cells, white blood cells and platelets, resulting in pancytopenia (hypersplenism).

Management

First-line treatment is with a non-selective beta-blocker (nadolol or propranolol) to reduce the pressure within the portal system. It is often used as primary prophylaxis once portal hypertension is diagnosed, and should always be considered for secondary prophylaxis after an episode of variceal bleeding.

Ascites

Ascites, the presence of fluid in the peritoneum, has two main pathogenic mechanisms, transudation and exudation.

- **Transudates** result from sequestration of fluid into the peritoneal space due to changes in hydrostatic and oncotic pressures across the peritoneum, or due to fluid retention:
  - Hydrostatic: these are the result of portal hypertension and resultant increases in the pressure in splanchnic vessels;
  - Oncotic: these are the result of lowered serum albumin as the synthetic function of the liver decreases;

- Fluid retention: renal hypoperfusion resulting from portal hypertension causes release of renin, and hence a secondary hyperaldosteronism; this results in salt and water retention and contributes to ascites.

- **Exudates** result from an inflammatory or neoplastic process at the peritoneal surface, causing increased production of peritoneal secretions. It is the former that is important in hepatic disease, although occasionally malignant processes that involve the liver may involve the peritoneal surface also.

In order to determine whether ascites is related to transudation or exudation the serum-to-ascites albumin gradient (SAAG) is calculated:

SAAG = Serum albumin concentration (g/l)
– Ascites albumin concentration (g/l)

A high gradient (>11 g/l) indicates the ascites is due to portal hypertension. A low gradient (<11 g/l) indicates ascites of non-portal hypertensive aetiology.

Management

- **General**:
  - Treatment of the underlying liver condition;
  - Improvement of nutritional status in order to maximize serum albumin.
- **Specific**:
  - Reduction of hydrostatic pressure in the splanchnic vasculature with diuretics, particularly spironolactone (an aldosterone antagonist);
  - Abdominal paracentesis (removal of ascitic fluid through a drain placed temporarily in the peritoneal space) when ascites volumes are large. There is an argument for the use of intravenous albumin replacement during paracentesis in order to reduce the haemodynamic consequences of fluid shifts: 10 g of albumin is given for each litre of ascites removed.

Management

Intractable ascites is defined as ascites not responding to aggressive diuretic use. In this setting the options are:

- Repeated paracentesis;
- Radiological placement of intrahepatic portal-venous shunts to reduce splanchnic pressure (transjugular intrahepatic portosystemic shunt [TIPS]);
- Surgical shunt placement (now rarely needed).

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is, as the name suggests, the spontaneous onset of bacterial infection of ascitic fluid in the setting of liver disease. Patients with the transudative ascites of liver disease with portal hypertension are particularly at risk of bacterial infection in the peritoneum because of the co-morbid loss of the defensive mechanisms present in normal peritoneal secretions, in particular opsonising proteins. Thus, the risk of SBP increases as the protein content of the fluid decreases, the greatest risk being in those with an ascitic albumin concentration <1 g/l.

The bacteria implicated in SBP are enteric organisms. Traditionally, three-quarters of SBP infections are caused by aerobic Gram-negative organisms (mostly *Escherichia coli*), and one-quarter are due to aerobic Gram-positive organisms (especially Streptococcal species). However, the percentage of Gram-positive infections may be increasing, related to quinolone resistance among Gram-positive bacteria.

Investigations

The *diagnosis* of SBP is by paracentesis and identification of ascitic neutrophils >250/mm^3. Gram stain and culture of ascitic fluid should also be performed. Culture is aided by direct inoculation of an aerobic and anaerobic blood culture bottle, each with 10 ml of ascitic fluid, at the time of collection.

Management

Empiric *therapy* is with:

- Intravenous third-generation cephalosporins, but may be guided by past culture and sensitivity results in the setting of recurrent SBP;
- Concomitant administration of intravenous albumin.

There may be a role for *prophylactic antibiotics* in patients at high risk:

- Ascitic albumin concentration <0.1 g/l;
- Past SBP;
- Patients with fluid protein <15 g/l and either Child–Pugh score of at least 9 or impaired renal function;
- Cirrhotic patients presenting with bleeding oesophageal varices.

Oesophageal and gastric varices

Chronic elevation of the portal pressure results in the formation of collateral venous tract formation between the portal circulation and the systemic venous system. The most troublesome site of collateral formation is around the proximal stomach and distal oesophagus (gastro-oesophageal varices). These varices result from collateral flow from the portal system, through the coronary vein of the stomach into the azygous vein (Figure 20.1). They lie submucosally and, with minimal trauma and resultant ulceration, can bleed into the GI tract. Varices are graded according to their size and the presence of overlying mucosal lesion (Box 20.1). The grade is a predictor of the likelihood of future variceal bleeding.

Management

Treatment of varices can take two forms:

- Primary prophylaxis, following diagnosis of varices but prior to the development of a bleeding complication;
- Secondary prophylaxis, instituted after an episode of bleeding.

Currently the favoured initial treatment for primary prophylaxis is with beta-blockers. The risk of variceal bleeding relates to the grade of varices and the severity of liver disease (Figure 20.1).

During an episode of variceal bleeding endoscopic treatment is required immediately following haemodynamic stabilization and airway protection:

Box 20.1 Grading for oesophageal varices.

Grade 1: Varices that collapse on inflation of the oesophagus with air
Grade 2: Varices between grades 1 and 3
Grade 3: Varices which are large enough to occlude the lumen

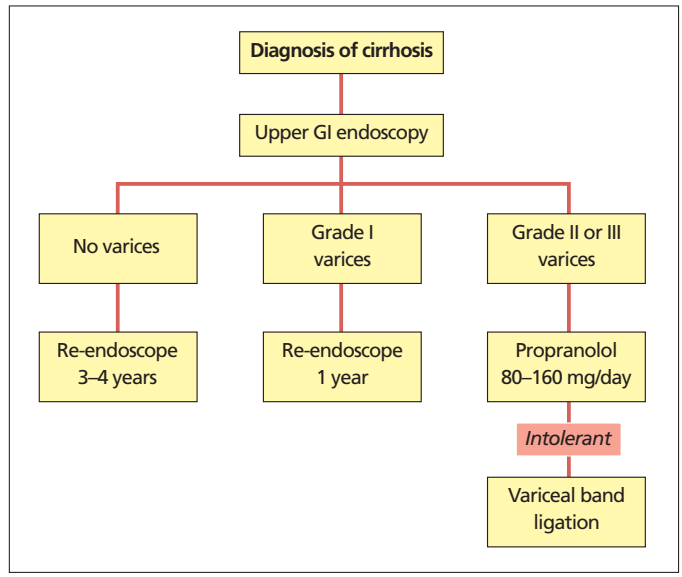

Figure 20.1 Primary management of oesophageal varices.

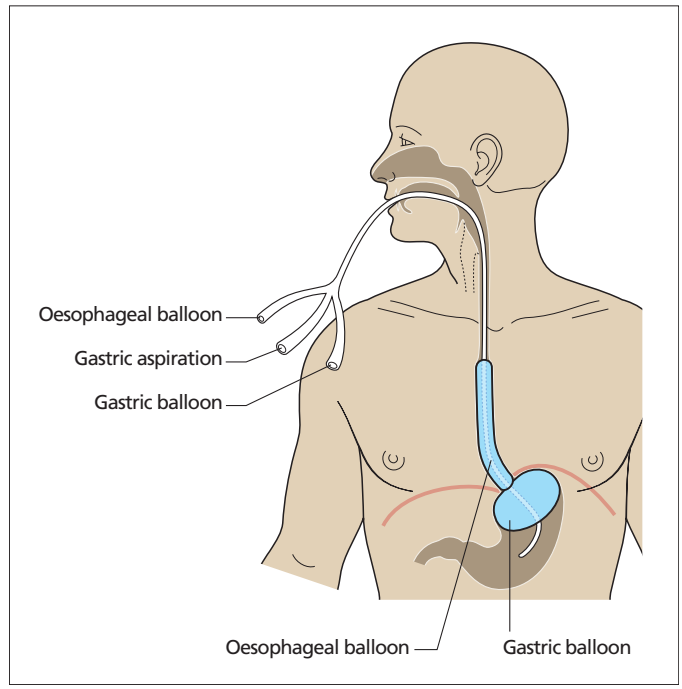

Figure 20.2 Sengstaken tube for tamponade of bleeding varices.

- Modality of first choice is band ligation:
- Second-line modalities are:
  - Sclerotherapy;
  - Splanchnic vasoconstrictors (vasopressin);
  - Sengstaken tube (an apparatus consisting of a tube with a balloon on the end which is inserted into the oesophagus to tamponade the bleeding vessel; Figure 20.2).

Secondary prophylaxis (Figure 20.3) following an episode of confirmed variceal bleeding is:

- Variceal band ligation in the first instance;
- Beta-blockers in combination with banding or alone;
- Endoscopic variceal injection of tissue glue or thrombin;
- Transluminal intrahepatic porto-systemic shunts (TIPPS) and surgical shunts are reserved for patients who do not respond to banding.

Hepatic encephalopathy

Hepatic encephalopathy results when toxic metabolites cannot be excreted by the diseased liver; they bypass the liver due to portosystemic shunts and produce direct effects on the brain. The mechanisms underlying this are thought to be multifactorial. Initially it was believed that direct toxic effects of ammonia on the brain were the main factor. However, more recently attention has focused on alterations in plasma amino acid composition leading to accumulation of 'false' neurotransmitters in the brain and increases in neuroinhibitory substances such as manganese, monoamines or endogenous opiates.

Investigations

The differential diagnosis of hepatic encephalopathy is wide (Box 20.2) and its diagnosis at presentation usually requires, in addition to the confirmation and grading of liver failure, exclusion of metabolic disease and toxins (or withdrawal effects) and head CT to exclude intracranial events. Subtle disturbances of cognition can be detected and followed using bedside and more specialised psychometric evaluation (Table 20.2).

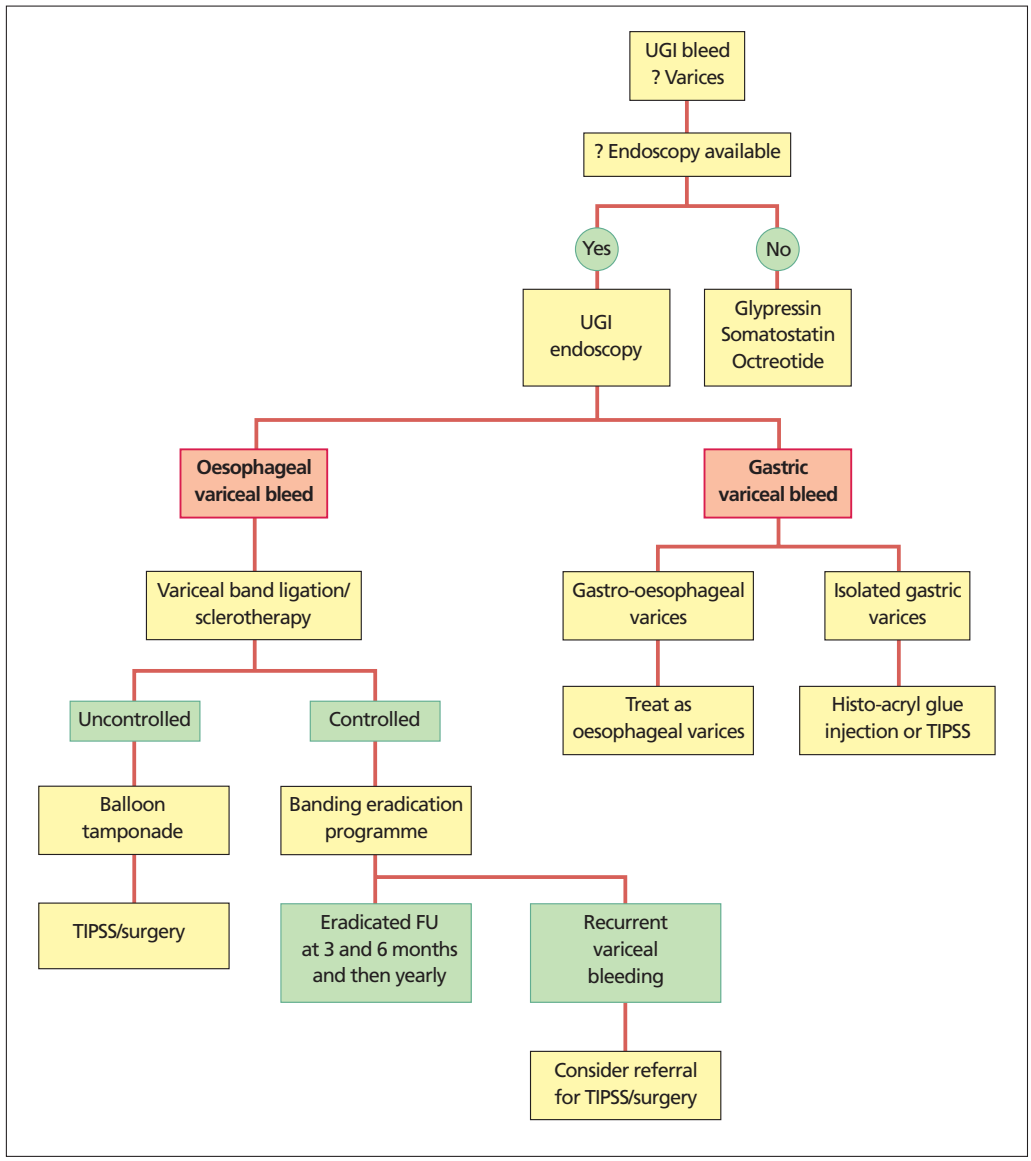

Figure 20.3 Secondary management of oesophageal varices.

Management

Frequently there are factors that precipitate the onset of encephalopathy and correction of these may reverse, or at least reduce symptoms. These factors can be classified as direct neurotoxic precipitants, promoters of ammonia formation and factors altering blood–brain barrier function (Table 20.3).

- The mainstay of therapy is the use of non-digestable disaccharides such as lactulose (given orally through a nasogastric tube or through retention enemas). The dose should be adjusted to accomplish three or four soft bowel movements each day.
- Reduction of protein in the diet may be reasonable in the short term but is not a long-term consideration.

Box 20.2 Differential diagnosis in hepatic encephalopathy.

Metabolic encephalopathies
- Diabetes (hypoglycaemia, ketoacidosis)
- Hypoxia
- Carbon dioxide narcosis

Toxic encephalopathies
- Alcohol (acute alcohol intoxication, delirium tremens, Wernicke–Korsakoff syndrome)
- Drugs

Intracranial events
- Intracerebral bleeding or infarction
- Tumour
- Infections (abscess, meningitis)

Encephalitis

Table 20.2 Grading of hepatic encephalopathy.

Grade	Level of consciousness	Personality and intellect	Neurological signs	Electroencephalogram abnormalities
0	Normal	Normal	None	None
Subclinical	Normal	Normal	Abnormalities only on psychometric testing	None
1	Day/night sleep reversal Restlessness	Forgetfulness Mild confusion Agitation Irritability	Tremor Apraxia Inco-ordination Impaired handwriting	Triphasic waves (5 Hz)
2	Lethargy Slowed responses	Disorientation to time Loss of inhibition Inappropriate behaviour	Asterixis Dysarthria Ataxia Hypoactive reflexes	Triphasic waves (5 Hz)
3	Somnolence Confusion	Disorientation to place Aggressive behaviour	Asterixis Muscular rigidity Babinski signs Hyperactive reflexes	Triphasic waves (5 Hz)
4	Coma	None	Decerebration	Delta/slow wave activity

- Traditionally, non-absorbable antibiotics were used to detoxify the colon and reduce the production of nitrogenous metabolites; however, because of toxic effects this is no longer commonly employed.
- Occasionally refractory encephalopathy is the main indicator for liver transplantation.

Hepatorenal syndrome

Renal dysfunction in chronic liver disease is often multifactorial: hypovolaemia, changes in renal perfusion, infection and use of nephrotoxic drugs. Hepatorenal syndrome (HRS) refers to acute, potentially reversible, oliguric renal failure resulting from intense intrarenal vasoconstriction in otherwise normal kidneys. It occurs both in patients with chronic or acute liver disease. The former comprises patients with cirrhosis, ascites and liver failure, the latter acute liver failure and alcoholic hepatitis. There are associated gross alterations in cardiovascular function and overactivity of the sympathetic nervous and renin–angiotensin systems, with resultant retention of sodium and water and renal vasoconstriction. It

Table 20.3 Precipitants of encephalopathy in chronic liver disease.

	Example	Mechanism	Treatment
Neurotoxins	Sedatives, tranquilizers, analgesics	Direct depressant action on brain	Avoid sedatives Lactulose
Increase in serum ammonia	Azotemia	Urea production in colon Excessive diuresis Prerenal azotemia	Lactulose Discontinue diuretics Volume expansion with albumin
	GI bleeding	Colonic protein load leads to ammonia Production Hypovolaemia	Lactulose Blood or plasma transfusionVolume expansion
	Excess dietary protein	Excess nitrogenous substances	Lactulose Reduce protein in diet
	Infection	Peripheral ammonia production Tissue catabolism leading to ammonia production	Treat infectionLactulose
	Constipation	Retention of ammonium in colon More efficient formation of ammonia by colonic bacteria	Laxatives (e.g. lactulose)
Disturbance of blood–brain barrier	Metabolic alkalosis	Diffusion of ammonia across blood–brain barrier	Treat underlying cause

can be classified into early (Type 1) and late (Type 2) hepatorenal syndrome (Table 20.4).

The diagnosis of HRS is one of exclusion (Box 20.3), and it should not be diagnosed until all potentially reversible causes of renal failure have been excluded or treated.

Management

In the first instance treatment is aimed at correcting reversible factors:

- Hypovolaemia;
- Infection;
- Presence of nephrotoxins.

Alternative initial treatment is obviously required in type 1 HRS:

- Vasoconstrictors, usually terlipressin, in combination with albumin administration;
- TIPSS improve renal function and may improve survival in type 1 HRS. This has not been shown in type 2 HRS, but TIPSS may be used to improve the refractory ascites often associated with type 2 HRS.

Box 20.3 Diagnostic hepatorenal syndrome criteria in cirrhosis.

- Cirrhosis with ascites
- Serum creatinine >133 μmol/l
- No improvement of serum creatinine (decrease to a level of 133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography

Liver transplantation is the only definitive treatment for HRS and remains the treatment of choice. It must be noted, however, that morbidity after liver transplantation is higher in patients with HRS than in those without HRS.

Table 20.4 Classification of hepatorenal syndrome (HRS).

Early (type 1) HRS	Late (type 2) HRS
Rapidly progressive: • Usually associated with acute deterioration of circulatory function • Characterised by arterial hypotension and activation of endogenous vasoconstrictor	Steady or slowly progressive course
Severe renal failure: Doubling of the initial serum creatinine concentrations to a level >226 µmol/l in <2 weeks	Moderate renal failure: Serum creatinine 133–226 µmol/l
May be associated with impaired cardiac and liver functions as well as encephalopathy	Typically associated with refractory ascites
May appear spontaneously, but often develops after a precipitating event, particularly SBP	Appears spontaneously, but can also follow a precipitating event
80% mortality at 2 weeks, only 10% survival at 3 months	70% survival at 3 months, 40% at 1 year

Hepatopulmonary syndrome

Pulmonary dysfunction in association with chronic liver disease is common, with up to 70% of patients complaining of shortness of breath. The differential diagnosis ofdyspnoea is extensive in this setting and includes all the common causes of pulmonary dysfunction in those without liver disease. The classical pulmonary condition occurring in chronic liver disease is termed hepatopulmonary syndrome (HPS). This occurs when intrapulmonary vasodilatation impairs arterial oxygenation. It has serious consequences in terms of increasing mortality in the setting of cirrhosis and may influence the frequency and severity of complications of portal hypertension. HPS may co-exist with other cardiopulmonary abnormalities.

Investigations

The diagnosis of HPS relies on the demonstration of:

- Liver disease or portal hypertension;
- Elevated age-adjusted alveolar–arterial oxygen gradient ($AaPO_2$); *and*
- Evidence of intrapulmonary vasodilatation.

Where pulmonary disease is suspected, arterial blood gas estimation should be performed and the alveolar–arterial oxygen gradient compared to age-controlled normal values. If hypoxia is demonstrated, more common pulmonary diseases must be screened for and adequately treated in the first instance (Figure 20.4).

The preferred test to demonstrate intrapulmonary vasodilatation and shunting is transthoracic microbubble contrast echocardiography. Echocardiography is performed by injecting agitated saline intravenously during normal transthoracic echocardiography, producing microbubbles that are visualised by ultrasonography. If an intracardiac shunt is present, contrast agent enters the left ventricle within three heart beats (early shunting). If intrapulmonary shunting characteristic of HPS is present, the left ventricle opacifies at least three heart beats after the right (delayed shunting).

In the presence of co-existing cardiac or pulmonary disease, establishing a diagnosis of HPS can be difficult. In the presence of cardiopulmonary disease, an estimate of the contribution of intrapulmonary shunting due to HPS, and its contribution to hypoxaemia, can be made using the macroaggregated albumin scan. In this test, radiolabelled aggregates of albumin measuring approximately 20 µm in diameter are infused into the venous system. In the presence of significant intrapulmonary shunting, a fraction of the macroaggregated albumin passes through the lungs and into the systemic circulation. Scintigraphy then reveals uptake in other organs in addition to the lung, allowing the calculation of the shunt fraction.

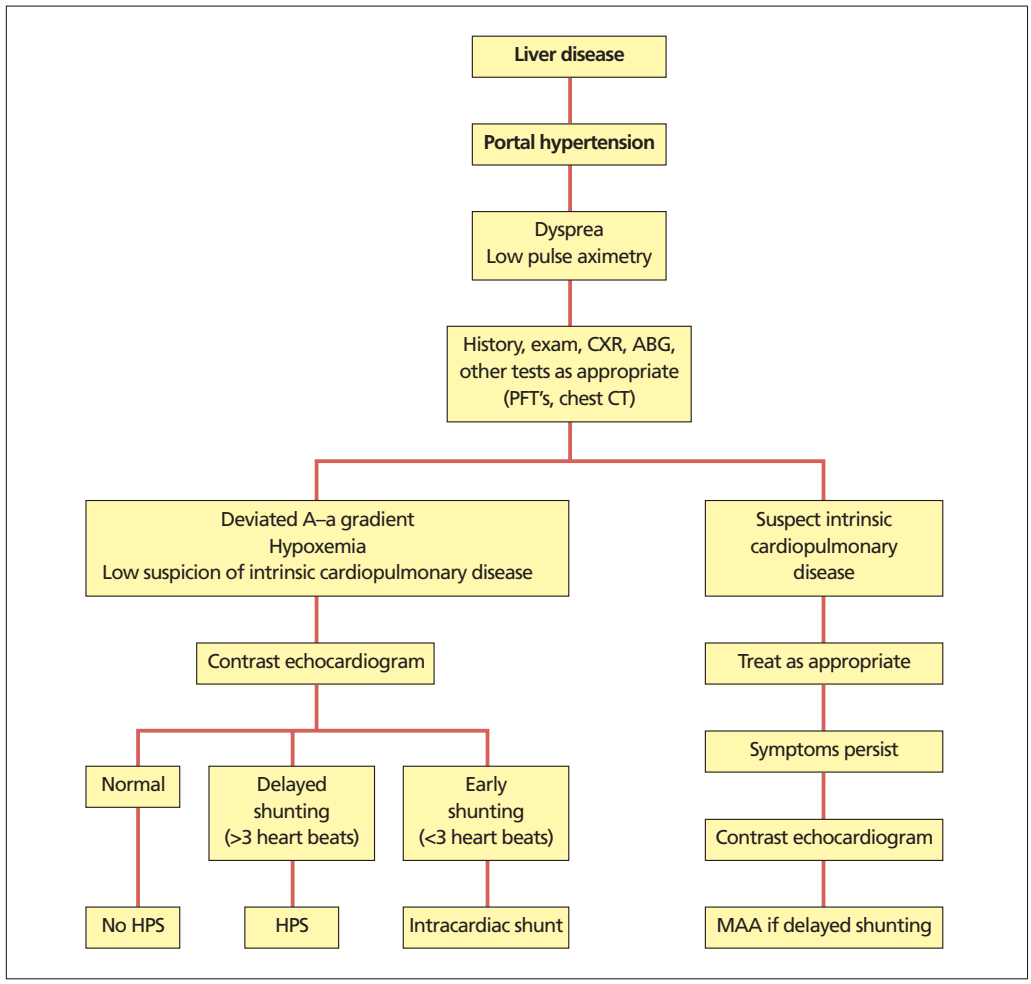

Figure 20.4 Diagnosis of hepatopulmonary syndrome (HPS). MAA, macroaggregated albumin scan.

Management

There are no effective medical therapies for HPS and liver transplantation is the only established effective therapy. Oxygen supplementation is the mainstay of supportive therapy for HPS patients with a $PaO_2 < 60$ mmHg or with exercise-induced oxygen desaturation.

21

Hereditary and congenital liver diseases

The exponential growth in genetic and molecular techniques over the last decade has led to improved understanding of the genetic and molecular mechanisms of inherited liver diseases. This has in turn led to genetic testing, allowing the diagnosis of genetic abnormalities before or soon after the onset of clinical disease. A description follows of the more common genetic conditions affecting the liver, and some of the important congenital conditions that do not appear to have a genetic basis.

Hereditary haemochromatosis

Aetiopathogenesis

Systemic iron overload is the hallmark of hereditary haemochromatosis (HHC). Iron deposits in many tissues at sufficient concentrations can cause clinically relevant damage to the liver, pancreas, heart, joints and pituitary. Mutations of the HHC gene (*HFE*) cause a defect in iron handling that leads to iron overload. However, the exact mechanism of this remains poorly understood despite description of the underlying genetic defect.

HFE codes for a major histocompatibility complex (MHC) class I protein that is expressed on many cells, including duodenal crypts. This MHC protein interacts with the transferrin receptor to facilitate iron uptake into cells and defects in it alter this interaction.

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Anton Emmanuel and Stephen Inns.

Haemachromatosis may result from a variety of causes other than heredity (Box 21.1).

Genetics

HHC is an autosomal dominant inherited condition, but genotype–phenotype correlations in HHC are highly variable, related to poorly understood genetic factors. However, female sex (and thus menstruation), conditions causing iron loss and age are implicated.

While the molecular mechanism has yet to be elucidated, the genetic defect is now well described. 80–90% of clinically diagnosed HHC patients are homozygous for a single G-to-A mutation in *HFE* which results in a cysteine-to-tyrosine substitution at position 282 (C282Y) of the gene product. Thus, this mutation accounts for the vast majority of disease. A second less common mutation (H63D) has been discovered; however, its role in causing clinically relevant iron overload is not clear as it is present in patients and controls at similar frequencies. While homozygotes for H63D do not exhibit significant iron overload, compound heterozygotes (i.e. C282Y/H63D) do have modest increased total body iron stores and progress to hepatic fibrosis or cirrhosis is rare.

Epidemiology

HHC is the commonest genetic disease in Caucasians with a prevalence of between 1 in 300 and 1 in 400. The fact that the carrier frequency is as high as 1 in 9 in some populations would predict a much higher disease prevalence, emphasising the complex genotype–phenotype association.

Box 21.1 Causes of haemochromatosis.

Genetic disorders

- Hereditary haemochromatosis (*HFE*, non-*HFE* and juvenile)
- Autosomal dominant haemochromatosis

Haematological disorders

- Thalassaemia major
- Sideroblastic anaemia

Others

- Increased dietery iron (African iron overload)
- Parenteral iron (e.g. multiple transfusions)
- End-stage alcoholic cirrhosis
- Neonatal haemochromatosis

Clinical features

These largely relate to iron deposition and depend on organ involvement.

- **General features**:
  - Lethargy;
  - Abdominal pain, episodic, can be severe (unclear cause, see below).
- **Hepatic features**:
  - Hepatomegaly;
  - Hepatic function is often well preserved and liver function tests may be normal despite high hepatic iron content and fibrosis;
  - Features of chronic liver disease may be present in advanced disease.
- **Extrahepatic manifestations**:
  - Diabetes mellitus occurs in relation to deposition of haemosiderin, predominately in pancreatic acinar cells, with resultant dense fibrosis. This damage occurs at a threshold tissue iron concentration similar to that of liver fibrosis. Diabetes develops in 30–60% of cases with advanced liver disease;
  - Cardiac manifestations are not uncommon and may be the presenting pathology in 5–15% of symptomatic patients. ECG abnormalities are seen in about 30% of patients. The most common cardiac complications are congestive heart failure, typically a dilated cardiomyopathy, and arrhythmias. If instituted early, phlebotomy results in improvement in cardiac manifestations;
  - Iron overload results in a variable destructive arthropathy. This is not improved by venesection and may progress despite maintenance of normal iron stores;
  - Pituitary gonadotrophs selectively express the transferrin receptor leading to accumulation of intracellular ferritin. Hypogonadotropic hypogonadism can thus occur early in the natural history of the disease.

Porphyria cutanea tarda (PCT) is associated with iron overload, and may occur in association with haemochromatosis.

Patients with iron overload are at increased risk of ***Yersinia enterocolitica*** **infection**. This organism is not commonly pathogenic in the absence of iron load because it does not possess a high-affinity iron-chelating system and is not able to obtain sufficient iron from the internal environment of the normal human body. It is speculated that at least some of the episodes of acute abdominal pain in HHC are related to infection with this organism.

Investigations

Clinicians should have a high index of suspicion for this common genetic condition.

- **Blood tests**:
  - Transferrin saturation;
  - Serum ferritin concentration (a very sensitive test for elevation of total body iron stores);
  - High serum iron;
  - High total iron-binding capacity;
  - However, false negatives may occur in menstruating women, ill patients (inflammatory and neoplastic conditions) and those with severe liver disease (viral hepatitis, non-alcoholic steatohepatitis and alcoholic liver disease), as serum ferritin is also an acute phase protein.
- **Genetic testing**:
  - Has replaced liver biopsy as the next test in suspected iron overload;
  - Both the C282Y and H63D mutations should be tested for – compound heterozygous states may act as a cofactor leading to fibrosis in conditions such as porphyria cutanea tarda, hepatitis C and steatohepatitis.
- **Liver biopsy**:
  - Useful in quantifying iron overload;
  - Useful in assessing hepatic fibrosis;
  - To calculate the hepatic iron index by dividing the hepatic iron concentration (in μmol/g dry

weight) by the age of the patients (in years). Values >1.9 are consistent with HHC.

Screening

Screening can be considered in three population groups:

1. Relatives of a proband with the disease (mandatory for all first-degree relatives and advisable to extend screening to second-degree relatives);
2. People undergoing a health check (probably cost-effective);
3. General population.

Screening should consist of a history and physical examination, measurement of transferrin saturation and serum ferritin. Assay for the C282Y mutation is undertaken in groups 2 and 3 if the transferrin saturation is >45% serum ferritin (because of the cost of genetic testing).

Screening for hepatocellular carcinoma

When cirrhosis is present, HHC patients have a 200-fold increased risk of hepatocellular carcinoma (HCC). HCC is the commonest cause of death in such patients. Patients who have developed HCC may present with unexplained weight loss, fever, nodular enlargement of the liver, variceal haemorrhage, ascites, jaundice and abdominal pain.

Patients who develop HCC usually have advanced hepatic fibrosis and cirrhosis. For this reason screening is reserved for patients with cirrhosis. Serum alpha-fetoprotein and serial ultrasound are used as in other forms of cirrhosis (see Chapter 28).

Management

Venesection is the mainstay of treatment. This should occur at weekly intervals until the haemoglobin concentration falls to 10.5 g/dl and does not recover immediately. *Monitoring of serum ferritin* shows a progressive decline during initial treatment, the aim being to keep the value within the low normal range (50–100 pg/l). Maintenance venesection is lifelong, approximately four times per year, but this needs to be individualised. Iron deficiency must be avoided (ferritin kept >20 pg/l).

In the presence of cardiac insufficiency, treatment is still with venesection, as it is the most efficient, safest and cheapest alternative, but may need to be in smaller amounts and less frequently. The iron-chelating agent desferrioxamine can be used when there is anaemia from other causes but at best removes only 10–20 mg of iron/day.

Prognosis

Prognosis is dependent on the presence of cirrhosis or diabetes. In the absence of these, life-expectancy is normal provided maintenance venesection is adhered to. Liver transplantation should be considered where there is end-stage liver disease or small HCCs. However, liver transplantation for HHC has been disappointing at least in part due to the degree of iron loading in these patients, as iron-loaded patients are at risk of infection as well as cardiac failure and arrhythmia.

Wilson's disease

Aetiopathogenesis

Wilson's disease is an autosomal recessive disorder caused by a defect in hepatic copper excretion, resulting in copper overload and copper deposition in various organs, including the liver, brain, kidneys and cornea, with resultant hepatic, neurological, psychiatric, haematological, renal, eye and other abnormalities.

In this condition copper is not incorporated into its carrier protein, caeruloplasmin, within hepatocytes. It is therefore not adequately excreted into bile and accumulates in the liver. Eventually it is released into blood and deposited in other tissues. Liver disease is attributed to oxidative stress resulting from the pro-oxidant properties of copper. There are high concentrations of copper in the hepatocellular mitochondria in hepatic copper overload and it may be that mitochondrial damage plays a role in the pathogenesis.

Genetics and epidemiology

The prevalence of Wilson's disease is 1 in 30 000 and the carrier frequency is 1 in 90. The abnormal *ATP7B* (conventionally called *WND*) gene is on chromosome 13. It encodes an intracellular membrane-spanning ATPase transporter with six copper-binding sites, which has a role in incorporating copper into caeruloplasmin.

Clinical features

Wilson's disease is highly variable and may present as:

- Acute hepatitis;
- Chronic liver disease;
- Fulminant liver disease;
- Progressive neurological disorder (often without clinically evident hepatic dysfunction);
- Psychiatric illness.

Patients usually become symptomatic between the ages of 6 and 45 years but may be diagnosed younger or older.

- **Hepatic presentation:** liver disease presentation is more common in children and adolescents. The features are often non-specific with fatigue, abdominal pain and anorexia:
  - Simple acute hepatitis: a self-limited clinical illness indistinguishable from autoimmune hepatitis, with:
    - Elevated serum aminotransferases;
    - Greatly increased serum IgG;
    - Detectable non-organ-specific autoantibodies, including antinuclear antibody and antismooth muscle (antiactin) antibody.
  - Repeated episodes of short-lived jaundice: largely asymptomatic, related to haemolysis;
  - Severe established chronic liver disease: typically, this occurs in late-stage patients with:
    - Acute Coombs-negative intravascular haemolysis;
    - Renal failure;
    - Kayser-Fleischer rings on slit-lamp examination;
    - Greatly elevated urinary copper excretion.
  - These patients do not respond to chelation treatment and require urgent liver transplantation. HCC rarely develops in Wilson disease.
- **Neurological presentation:** a predominately neurological presentation usually occurs in older teenagers or adults. There are two predominant patterns of involvement:
  - Movement disorders, including tremors, poor co-ordination and loss of fine motor control;
  - Rigid dystonia with mask-like facies, rigidity and gait disturbance;
  - Pseudobulbar involvement is more common in older patients and may result in dysarthria, drooling, and swallowing problems. Seizures may occur.
- **Psychiatric presentation:** a purely psychiatric presentation occurs in 20% of patients and the symptoms are highly variable. Depression is common and neuroses, including phobias and compulsive behaviours, are reported. Pure psychosis is uncommon. Intellectual deterioration may also occur.
- **Other manifestations:**
  - Fatigue, malaise, arthropathy and rashes;
  - Renal dysfunction;
  - Vitamin D-resistant rickets with severe renal dysfunction;
  - Haemolysis related to copper release into the bloodstream;
  - Cholelithiasis may occur with repeated haemolysis;
  - Pancreatitis;
  - Endocrine: hypoparathyroidism, amenorrhoea, testicular dysfunction, repeated spontaneous abortion;
  - Kayser–Fleischer rings due to copper accumulation in Decemet's membrane in the posterior cornea;
  - Sunburst cataracts, in approximately 20% of patients;
  - Cardiomyopathy and cardiac arrhythmias (rare);
  - Rhabdomyolysis (very rare).

Investigations

Essential to the diagnosis of this rare condition is a high index of suspicion in the appropriate clinical setting. All patients being investigated for suspected autoimmune hepatitis should be tested for Wilson's disease because of the similarities in clinical features between the two.

Blood tests

The hallmark of Wilson disease is a low caeruloplasmin. This carrier protein binds most of the copper in plasma (> 90%). The normal adult serum concentration of caeruloplasmin is 200–600 mg/l and in most patients with Wilson's disease this is greatly reduced (typically <50 mg/l).

False negatives may occur:

- Difficulties with laboratory assays;
- Hepatic inflammation (as caeruloplasmin is elevated in inflammatory conditions);
- Pregnancy;
- Exogenous oestrogen.

False positives may occur:

- Decompensated cirrhosis of any cause or acute liver failure;

- Protein-losing enteropathy;
- Nephritic syndrome;
- Malnutrition;
- Heterozygotes for Wilson disease (10% of whom have low levels).

Other tests

- Urinary copper excretion increases (24-h urinary collections are typically >100 µg/24 h).
- Liver biopsy determines hepatic copper concentration (a value >250 µg/g dry weight is considered diagnostic, values <40 µg/g make Wilson's disease unlikely).
- Genetic testing is complex, with almost 300 mutations in the *ATP7B* gene, and most patients are compound heterozygotes. Where biochemical findings are equivocal, demonstration of two abnormal alleles is necessary for diagnosis. Mutational analysis can allow presymptomatic diagnosis of the siblings of affected individuals, including those whose biochemical testing is negative (thus permitting early chelation therapy).

Management

The mainstay of treatment is chelation therapy. First-line treatment consists of penicillamine which greatly increases urinary excretion of copper and induces tissue metallothioneins. Its use is limited by common mild side-effects (skin rashes, loss of taste, GI upset, diarrhoea, arthralgias). Severe side-effects are rarer (proteinuria, leucopenia or thrombocytopenia, and rarely aplastic anaemia). 30% of patients with Wilson's disease develop some side-effect of penicillamine, leading to a change of treatment. Deterioration in neurological status occurs initially after starting penicillamine in up to 50% of patients who present with mainly neurological symptoms. Most, but not all, recover with continued use. Pyridoxine 25 mg/day is given in conjunction with penicillamine.

Second-line treatment for patients intolerant of penicillamine is with Trien (trientine). Side-effects are rare apart from occasional gastritis, iron-deficiency (due to chelation of dietary iron) and sideroblastic anaemia. Neurological worsening is much less common than with penicillamine. Finally, zinc can be used as chelation and, apart from gastritis, has few adverse effects.

With all treatment modalities compliance and efficacy should be checked by measuring 24-h urinary copper excretion every 6–12 months; FBC and urinalysis should be monitored regularly. With effective and early treatment, most patients are well and live normally. Some reduction of dietary copper is probably also beneficial.

Alpha-1-antitrypsin deficiency

Aetiopathogenesis

Alpha-1-antitrypsin is a protease inhibitor that controls tissue degradation by inhibiting a large number of proteases, including trypsin, plasmin, thrombin, neutrophil elastase and proteinase 3. It is predominately produced in the liver with some production in the monocytes and bronchoalveolar macrophages also. Deficiency of alpha-1-antitrypsin is one of the commonest hereditary disorders in Caucasians.

Liver disease in this condition is mediated by accumulation of aggregated alpha-1-antitrypsin within the hepatocyte endoplasmic reticulum, visible as periodic acid-Schiff (PAS)-positive inclusion bodies on liver histology. The liver cell injury of alpha-1-antitrypsin deficiency is directly related to this accumulation, and not to a deficiency of elastase inhibitory capacity. This is evidenced by the fact that individuals with a genetic mutation that aborts alpha-1-antitrypsin production (hence no detectable alpha-1-antitrypsin in their plasma) and lack of the PAS-positive inclusion bodies, do not develop liver disease.

By contrast lung injury is a result of loss of protease inhibition; chronic obstructive respiratory disease (CORD) due to emphysema is the most prevalent clinical disorder associated with alpha-1-antitrypsin deficiency. Emphysema is due to loss of the normal antiproteolytic defences against elastase. The resultant degradation of elastic fibres with loss of elastic recoil in the lung and air-flow obstruction lead to emphysema, markedly exacerbated by smoking as the elastase burden is increased by recruitment of both neutrophils and macrophages.

There is an association between small-vessel systemic necrotising vasculitis and severe alpha-1-antitrypsin deficiency. It seems likely that the association is due to a loss of the protective effects of alpha-1-antitrypsin in small-vessel vasculitis rather than a direct causative effect.

Table 21.1 Genetic variants of alpha-1-antitrypsin deficiency.

Variant	% Normal serum alpha-1-antitrypsin levels	Clinical features
PiZZ	15–20%	20–40% cirrhosis in adulthood Onset of COPD-related dyspnoea aged 30–40 in smokers and 10–15 years later in non-smokers Associated with small-vessel vasculitides
PiSZ	30–40%	Probable association with end-stage liver disease in combination with several aetiologies (in particular hepatitis C virus and alcohol-related liver disease) Increased risk COPD Associated with small-vessel vasculitides
PiMZ	50–60%	Probable association with end-stage liver disease in combination with several aetiologies No predisposition to early development of COPD Associated with small-vessel vasculitides
PiSS	60%	Normal
PiMM	Normal	Normal

Genetics

Alpha-1-antitrypsin is encoded by a single gene located on chromosome 14. There are at least 75 different identified allelic variants and inheritance is codominant; thus each parental allele contributes its own gene product in the individual. Given the complexity of the genotypic abnormalities, a phenotypic classification system is used which is based on the isoelectric properties (on protein electrophoresis) of the protease inhibitor (Pi) produced. Variants that result in faster-moving proteins are identified by letters near the beginning of the alphabet, the slowest-moving allele being designated PiZ. The important genetic variants and their clinical consequences are summarised in Table 21.1.

Clinical features of liver disease

Childhood-onset liver disease

Alpha-1-antitrypsin deficiency is the most common genetic cause of liver disease in infants and children and the most common metabolic error for which liver transplantation is indicated. The majority (70%) of neonates with homozygous (PiZZ) alpha-1-antitrypsin deficiency have abnormal LFTs and a significant minority (10–20%) develop clinically important liver disease. They present with the 'neonatal hepatitis syndrome':

- Pruritus;
- Hepatomegaly;
- Conjugated hyperbilirubinaemia;
- Increased serum aminotransferase;
- Cholestasis can be marked and the disease can be confused with hepatic biliary atresia.

Alpha-1-antitrypsin states (PiMZ and PiSZ) cause partly self-limiting predominantly subclinical liver involvement in 10–20% of affected children and adolescents.

The disease usually resolves spontaneously within 6 months, although mild biochemical abnormalities persist in a proportion. In a small minority (<5%), the liver disease does not subside, progressing to cirrhosis and liver failure.

Adult-onset liver disease

The phenotypic expression of alpha-1-antitrypsin deficiency-related liver disease in adults is variable. There is a high risk of cirrhosis and HCC in adults with severe alpha-1-antitrypsin deficiency (PiZZ). Approximately 40% and 15% of alpha-1-antitrypsin-deficient adults develop cirrhosis and HCC, respectively. Patients may or may not have a history of neonatal liver disease. Prognosis is poor in patients with cirrhosis, partly due to concomitant emphysema.

In adults intermediate deficiency has been associated with chronic liver disease in combination with concomitant liver pathology, in particular with hepatitis C virus and alcohol-related liver

disease. The mechanism for this may be that the concomitant condition promotes retention of the abnormal protein in the hepatocyte endoplasmic reticulum.

Investigations

- Alpha-1-antitrypsin deficiency can be diagnosed by a marked reduction or absence of the alpha-1-globulin band in an agarose gel electrophoresis.
- Serum or plasma concentrations can be measured but are not accurately indicative of the phenotype because of the large variability in serum levels.
- Phenotype is usually assessed using isoelectric focusing (IEF) to ascertain the isoelectric band focusing patterns of the Pi variants. Enzyme-linked immunosorbent assay (ELISA) and DNA-based methods can be used, particularly for screening large populations. At least the first-degree relatives of patients found to have alpha-1-antitrypsin deficiency should be screened in order to detect the 25% of siblings who will be homozygotes at an early asymptomatic stage (although the only preventive measure likely to prolong survival is smoking cessation).

Management

Monitoring

- All patients diagnosed with alpha-1-antitrypsin deficiency should be regularly assessed with tests of liver function. If cirrhosis is established, screening for HCC may be appropriate.
- Monitoring for renal disease and vasculitis in both heterozygotes and homozygotes.
- Chest X-ray and pulmonary function assessment (especially in smokers).

Specific

Attempts to increase serum levels of alpha-1-antitrypsin may impact on the progression of pulmonary disease, but will have no beneficial effect on liver disease as the pathogenic abnormality is related to intrahepatocytic accumulation of abnormal protein rather that reduced Pi activity.

- The androgen danazol and the oestrogen antagonist tamoxifen increase synthesis of alpha-1-antitrypsin slightly but not sufficiently to have a beneficial effect.
- Purified human alpha-1-antitrypsin can be given by infusion. Its use is mainly in patients with progressive emphysema and vasculitis.
- While the primary pulmonary defect is emphysema, there may be a reversible obstructive component that responds to bronchodilator treatment.
- Orthotopic liver transplantation is curative for both liver disease and the alpha-1-antitrypsin deficiency state, as the recipient assumes the donor's phenotype. It is reserved for advanced liver disease in the absence of HCC and where preoperative evaluation of lung function is satisfactory. With this careful selection, survival rates in children are close to 90% at 1 year and 80% at 5 years. Survival in adults is lower, due partly to concomitant emphysema.
- At present, somatic gene therapy is not an available alternative.

Alagille's syndrome

Aetiopathogenesis

Alagille's syndrome (AS) is an inherited disease causing cholestasis in conjunction with cardiovascular, facial, ocular, skeletal and neurodevelopmental abnormalities. It is also known as arteriohepatic dysplasia. Cholestasis is a result of marked paucity of interlobular bile ducts. The mechanisms by which these abnormalities come about are unknown, but the genetic defect has been described.

Genetics

AS is an autosomal dominant disease, but in up to 15% of cases it is due to a new mutation. There is a large variability in expression of the disease, even within affected families. The incidence of AS in mixed Caucasian populations is 1 in 100 000 live births with no gender differences. The genetic defect is a mutation of the *JAG1* gene on chromosome 12. It encodes a protein belonging to the family of Notch ligands, which are regulatory receptors of the signalling pathway controlling cell fate decisions in a number of developmental processes.

Clinical features

- AS characteristically presents as prolonged neonatal cholestasis (jaundice, pale stools,

dark urine). In this setting it must be differentiated from biliary atresia in particular.
- Presentation in older children is with features of chronic liver disease, pruritus and xanthomata.
- It is common for adults to go undiagnosed until a related index case is diagnosed, but questioning may reveal a history of pruritus as a child.

HCC has been reported in AS with and without cirrhosis.

Extrahepatic features

- Facial appearance:
  - Triangular face, broad forehead, saddle-shaped nose, widely spaced deep set eyes, pointed chin.
- Vascular abnormalities (85–100%):
  - Commonly peripheral pulmonary stenoses of no clinical significance;
  - Occasionally pulmonary vascular hypoplasia or severe pulmonary artery stenosis.
- Severe vascular lesions often occur with other congenital heart anomalies:
  - Tetralogy of Fallot, truncus arteriosus, septal defects, systemic vascular abnormalities, narrowing of the abdominal aorta.
- Increased risk of intracranial haemorrhage (particularly in young adults):
  - Related to abnormalities in clotting secondary to chronic liver disease or structural abnormalities in intracranial vessels.
- Other manifestations:
  - Spinal problems:
    - Butterfly vertebrae; – Occult spina bifida.
  - Characteristic eye changes in up to 90%:
    - Prominent line in the anterior chamber (Schwalbe's line);
    - Ocular problems secondary to chronic cholestasis.
  - Renal abnormalities;
  - Neurodevelopmental delay;
  - Malnutrition and failure to thrive.

Investigations

Because of the variability of expression of the disease, diagnosis remains phenotypic and is based on the occurrence of cholestasis with histological paucity of interlobular bile ducts, plus two of four extrahepatic features (characteristic facies, cardiac murmur, vertebral anomalies, posterior embryotoxin.

Evaluation of all possible manifestations of the disease is mandatory (nutritional assessment, liver biochemistry and biopsy, cardiovascular testing, renal function, slit-lamp eye examination, spinal X-rays, serum bile acids, cholesterol and triglycerides).

A complete genetic evaluation, including family pedigree (with examination of family members), molecular genetic studies, cytogenetic studies and genetic counselling, is required.

Management

- Management of the consequences of chronic cholestasis is of the utmost importance:
  - Careful provision of adequate calories, protein and fat-soluble vitamins (A, D, E and K);
  - Management of mineral deficiencies.
- Severe hyperlipidaemia is associated with early atherosclerosis and can be managed to a degree with cholestyramine and ursodeoxycholic acid (UDCA).
- Treatment of pruritus is with antihistamines, but if intractable may respond to biliary diversion and occasionally liver transplantation.

Prognosis

The natural history of AS is variable, with a 74% 10-year survival. Complex cardiovascular anomalies are the major cause of early mortality, hepatic complications the cause of late morbidity and mortality.

Hereditary hyperbilirubinaemias

In an infant or child presenting with jaundice due to hyperbilirubinaemia, the differential diagnosis is broad. Determination of the concentrations and proportions of conjugated and unconjugated bilirubin is important (Figure 21.1). Once other forms of liver disease have been excluded, and particularly in the presence of a family history of hyperbilirubinaemia, the hereditary hyperbilirubinaemias should be considered (Table 21.2).

While conjungated hyperbilirubinaemia is almost always a consequence of underlying liver disease, and is harmless in itself, unconjugated bilirubin causes neurotoxicity by inhibiting RNA and carbohydrate as well as protein synthesis in the brain when it is persistently elevated.

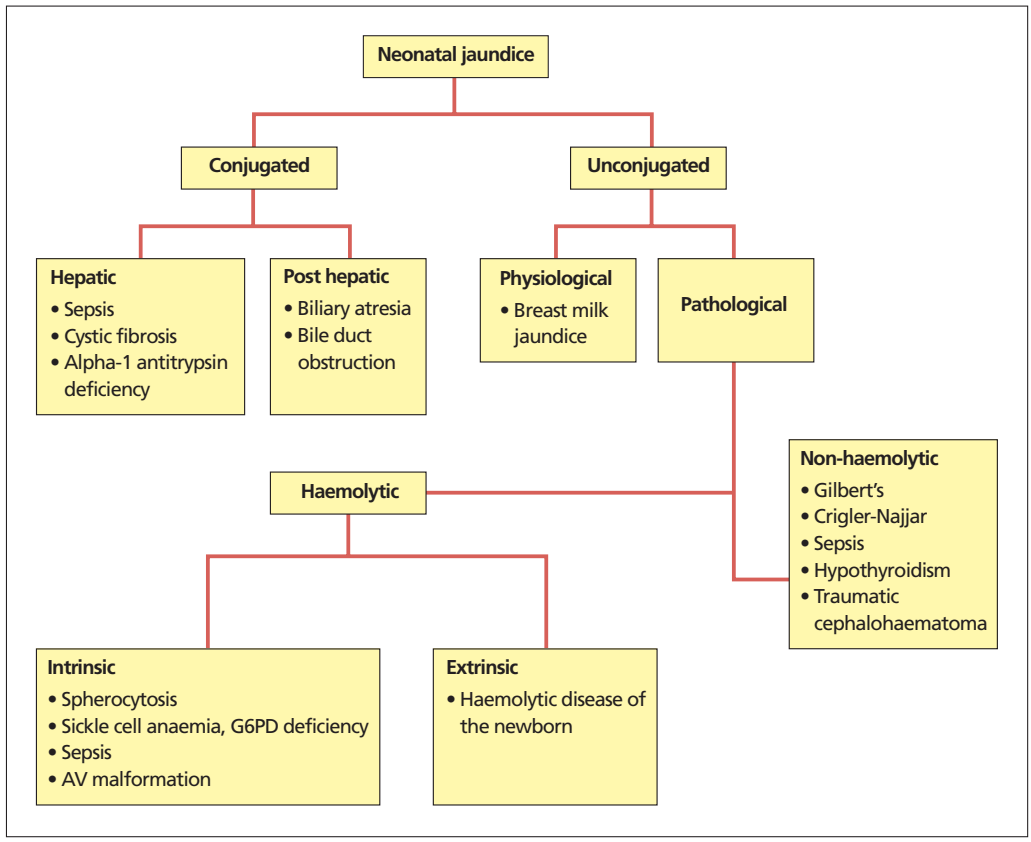

Figure 21.1 Causes of neonatal jaundice.

PHYSIOLOGY OF BILIRUBIN METABOLISM

Degradation of haemoglobin, and other haem proteins, produces bilirubin. This is tightly but reversibly bound to plasma proteins, in particular albumin. On reaching the hepatocyte membrane, bilirubin dissociates from albumin and enters the hepatocyte via a membrane carrier-mediated process. In the cell it is bound to glutathione S-transferase, which acts as the intracellular store for bilirubin. In the endoplasmic reticulum, bilirubin is conjugated by bilirubin uridine-diphosphate glucuronosyltransferase (B-UGT) for efficient elimination in bile. There are two main families of B-UGT, both of which derive from a gene complex on chromosome 2. The vast majority of bilirubin conjugates are excreted in the bile as bilirubin diglucuronide (80%) and bilirubin monoglucuronide (15%). Unconjugated bilirubin accounts only for 1–2% of bilirubin excreted into the bile.

Autoimmune polyglandular syndromes

The autoimmune polyglandular syndromes (APS) are autoimmune syndromes with symptoms affecting gland-bearing tissues, and as such the gut is often involved (Table 21.3). A single gene defect is responsible for APS type 1. Diagnosis is based on the pattern of glandular disease. APS type 1 is associated with a low but recognised incidence of GI disease.

Table 21.2 Clinical features of the familial hyperbilirubinaemias.

	Aetiology	Clinical features	Diagnosis	Treatment
Familial unconjugated hyperbilirubinaemia syndromes				
Crigler-Najjar I (CNS-I)	Autosomal recessive Consanguinity common Several genetic mutations identified Deficiency of both UGTI and UGT2 Massive bilirubin deposition in tissues including: • Kidney • Endocardium • Intestinal mucosa • Brain	Severe, chronic unconjugated hyperbilirubinaemia: • Onset after birth • Bilirubin between 342 and 599 μmol/l Lesser degrees of hyperbilirubinaemia may not develop neurological symptoms until second decade Cerebellar symptoms may predominate	No detectable B-UGT1 activity on assay of hepatic tissue Phenobarbital challenge: • CNS-II decrease bilirubin levels by >30% • CNS-I have no response	Definitive treatments • OLT curative (survival similar to that of OLT for other indications) Alternatives to OLT: • Auxiliary liver transplantation • Hepatocyte transplantation • Gene therapy Temporary treatments: • Phototherapy • Exchange transfusion • (CNS-I does not respond to phenobarbital) • Tin-containing compounds (inhibit haem oxygenase, thus decreasing haem degradation and bilirubin production) *Note*: only 1–2% functioning hepatocytes necessary for bilirubin conjugation
Crigler-Najjar II (CNS-II)	Autosomal recessive Genetics less well defined	Hyperbilirubinaemia less severe: • Rarely exceeding 342 μmol/l • Increased to >342 μmol/l during illness Icterus: • Present in 50% within the first year of life • Can occur as late as 30 years • Non-specific neurological symptoms as late as 50 years	Activity of B-UGTI reduced to <10% Bilirubin monoglucuronide in bile: • Collected by small bowel intubation • In CNS-I it is absent • Not significant enough to allow differentiation with certainty	Adequately treated with phenobarbital Phototherapy may be needed as an adjunct Mechanisms for the action of phenobarbital include: • Induction of binding proteins and mobilization of bilirubin • Enhanced B-UGTI transcription and activity • Atrophic effect on the endoplasmic reticulum

Gilbert's syndrome	Reduction in hepatic bilirubin clearance to approximately one-third normal Proposed mechanisms: • Defective uptake into the hepatocyte, • Intracellular binding • Conjugation Hereditary basis • Inherited either as an autosomal dominant or autosomal recessive Likely Gilbert's syndrome represents a heterogeneous group of disorders	Mild, chronic unconjugated hyperbilirubinaemia: • Absence of haemolysis • No hepatic injury Common (prevalence 3–12%): • Most often adolescents and young adults • Males > females Approx 1/3 asymptomatic except for jaundice Non-specific symptoms • Fatigue • Weakness • Abdominal discomfort • Malaise • All felt to be incidental Degree of hyperbilirubinaemia fluctuates: • Usually 52 μmol/l • May reach levels as high as 137 μmol/l Triggered by • Physical stress • Fatigue • Intercurrent illness • Alcohol intake	Other hepatic and haematological diseases excluded by history, physical examination and laboratory studies If no abnormalities develop after 12–18 months of follow-up, diagnosis almost certain Provocative testing: • Caloric deprivation (400 kcal/day) for 48–72 h, followed by a subsequent rise in plasma unconjugated bilirubin levels • Nicotinic acid tolerance test	Only treatment necessary is reassurance and education

(*continued*)

Table 21.2 Clinical features of the familial hyperbilirubinaemias (*continued*)

	Aetiology	Clinical features	Diagnosis	Treatment
Familial conjugated hyperbilirubinaemia syndromes				
Dubin–Johnson syndrome	Autosomal recessive Worldwide distribution Male = female Dubin–Johnson syndrome more common than Rotor syndrome Mechanism: • Defective hepatic secretion into the bile • Caused by the absence of the *MRP* (multidrug resistance protein) gene	Mild, predominantly conjugated hyperbilirubinaemia: • 34–120 μmol/l, • >50% conjugated. • Level of bilirubin • Fluctuates • Oral contraceptives and pregnancy exacerbate hyperbilirubinaemia Vague, non-specific abdominal complaints probably incidental Hepatosplenomegaly rarely	Cholescintigraphy: • ^{99m}Tc-HIDA scan • Intense prolonged visualisation of the liver • Delayed visualisation of gallbladder and bile ducts Differentiation of Dubin–Johnson syndrome from Rotor syndrome and other hepatobiliary diseases: • Urine coproporphyrin patterns after d-ALA administration • Bromsulphalein (BSP) clearance Oral cholecystography (gallbladder visualised in Rotor syndrome, but not Dubin–Johnson syndrome)	Benign disorders, without need for treatment
Rotor syndrome	Autosomal recessive Worldwide distribution Male = Female Mechanism: • Decreased intracellular storage of bilirubin • Excretion of bilirubin is moderately decreased	Asymptomatic except for jaundice		

OLT, Orthotopic liver transplantation; B-UGT1, bilirubin uridine-diphosphate glucuronosyltransferase 1.

Table 21.3 Clinical features of the autoimmune polyglandular syndromes.

	Aetiology	Clinical features and diagnosis
Autoimmune polyglandular syndrome type I (APS1) Autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED)	Autoimmune disease Mendelian inheritance: • Defects in a single gene • 100% penetrance • Gene on chromosome 21 • Named autoimmune regulator 1 (*AIRE-1*) or *APECED* gene Lack of HLA dependence Male = female High prevalence in Iranian Jews, Finnish and Sardinian people	First clinical manifestation typically in first decade of life Progressively new disease components may manifest even in the fifth decade Other associated immune disorders are frequently found Three groups of disease components: 1. Mucocutaneous candidiasis 2. Autoimmune tissue destruction, predominantly of endocrine glands: ○ Hypoparathyroiditis (89%) ○ Adrenocortical insufficiency (70%) 3. Ectodermal dystrophy ○ Dystrophy of the nails ○ Enamel hypoplasia ○ Alopecia ○ Keratopathy Associated GI disease: • Intestinal malabsorption in about 18% of patients • Autoimmune hepatitis in about 12% of patients Diagnosis: two of the following three (however, if APS1 in a brother or a sister, one disease component is sufficient): • Addison disease • Hypoparathyroidism • Chronic mucocutaneous candidiasis
Autoimmune polyglandular syndrome type 2	Autosomal dominant mode of transmission Polygenic Female preponderance Linkage to HLA-DR3 and DR4 Far more common than APS1	Adult onset of disease Associated autoimmune manifestations: • Vitiligo • Gonadal failure • Alopecia • Pernicious anaemia Diagnosis: • Addison disease, autoimmune thyroid disease and/or insulin-dependent diabetes mellitus (Schmidt's syndrome) • Occurring in a single patient not affected by hypoparathyroidism or candidiasis
Autoimmune polyglandular syndrome type 3	Heterogeneous	Autoimmune thyroid disease and the presence of at least one second autoimmune disorder in the absence of Addison disease

Table 21.4 Clinical features and investigation findings of the porphyrias.

Condition	Symptoms	Blood findings	Urine findings	Stool findings
Plumboporphyria	Neurological	Protoporphyrin IX	ALA, coproporphyrin III	
Acute intermittent porphyria (AIP)	Neurological		ALA, porphobilinogen	
Congenital erythropoeitic porphyria (CEP)	Skin	Uroporphyrin I	Uroporphyrin I	Coproporphyrin I
Porphyria cutanea tarda (PCT)	Skin		Uroporphyrin I	Isocoproporphyrin
Hereditary coproporphyria	Neurological and skin		ALA, porphobilinogen, coproporphyrin III	Coproporphyrin III
Variegate porphyria	Neurological and skin		ALA, porphobilinogen, coproporphyrin III	Protoporphyrin IX
Erythropoeitic porphyria	Skin	Protoporphyrin IX		Protoporphyrin IX

ALA, amino laevulonic acid.

The porphyrias

These are rare disorders of haem biosynthesis, characterised as either hepatic or erythropoeitic (depending on the site of excess porphyrin production). They are mostly autosomal dominant inherited partial enzyme deficiencies. The key role of environmental factors in causing symptoms explains why penetrance is poor: alcohol, iron excess, oestrogens and hepatitis C infection are the commonest environmental triggers.

Clinical features

The porphyrias usually present after puberty. Two presentations are described (Table 21.4):

- Photosensitive *skin* features:
  - Pain;
  - Erythema, bullae;
  - Hirsutism and hyperpigmentation.
- Acute relapsing–remitting *neurological* features (triggered by anticonvulsants, oral contraception, alcohol, fasting):
  - Acute abdominal pain;
  - Autonomic symptoms (hypertensive headaches, constipation);
  - Peripheral neuropathy;
  - Psychiatric manifestations;
  - Inappropriate ADH secretion.

Investigations

Table 21.5 illustrates the blood, urine and stool features of the porphyrias. Additionally, the identification of the genes of the haem biosynthesis pathway has allowed genetic screening of family members, although there are a large number of mutations for each porphyria.

Management

- **Cutaneous forms**:
  - Avoid skin exposure and trauma, use of barrier creams;
  - In porphyria cutanea tarda, venesection or chloroquine can be helpful.
- **Neurological forms**:
  - Avoidance of triggers;
  - Intravenous glucose (calories reduce abnormal enzyme activity, helping terminate attacks);
  - Administration of haem (reduces metabolite excretion and accelerates recovery).

Glycogen storage diseases

The glycogen storage diseases represent a broad range of clinical entities brought about by

Table 21.5 Clinical features of the glycogen storage diseases.

	Clinical features	Treatment

Type 1 glycogen storage disease	Impaired glucose-6-phosphatase system activity:
	• Excessive accumulation of glycogen and fat
	• inadequate hepatic glucose production via glycogenolysis and gluconeogenesis
	Classical presentation:
	• Neonatal period with hypoglycaemia and lactic acidosis or 3–4 months of age with hepatomegaly and/or hypoglycaemic seizures
	• Doll-like faces with excess adipose tissue in cheeks
	• Short stature
	• Protuberant abdomen
	• Kidneys often symmetrically enlarged
	• Liver transaminases normal or only slightly elevated
	• Hypoglycaemia and lacticacidaemia can occur after a short fast
	• Hyperuricaemia often present
	• Intermittent diarrhoea
	• Bruising and expistaxis – prolonged bleeding time as a result of impaired platelet aggregation and adhesion
	• Significant elevation of triglycerides:
	  ○ Cholesterol and phospholipids elevated, but less prominently
	  ○ Skin xanthomas
	  ○ Retinal changes associated with hyperlipidaemia
	Note: some patients do not show all the classical symptoms and/or have only relatively mild symptoms. In rare cases asymptomatic
	Liver histology:
	• Universal distension of hepatocytes by glycogen and fat
	• Lipid vacuoles are large and prominent
	Long-term consequences:
	• Growth impaired
	• Puberty frequently delayed
	• Gout starts around puberty
	• Increased risk of pancreatitis
	• Hepatic adenomas
	• Hepatomas
	• Heart failure secondary to pulmonary hypertension
	• Osteoporosis
	• Renal disease common
	• Type Ib glycogen storage:
	  ○ Additional findings of neutropenia and impaired neutrophil function
	  ○ Ulceration of oral and intestinal mucosa common
	  ○ Inflammatory bowel disease reported
		Main aim to prevent hypoglycaemia
		Dietary therapy:
		• Nocturnal nasogastric infusion of glucose
		• Orally administered uncooked cornstarch
		Careful control of glucose during illness and perioperatively essential
		Allopurinol to reduce the levels of uric acid
		Liver transplantation:
		• Only if other treatments fail or
		• If there has been malignant transformation of an adenoma
		Kidney transplantation in renal failure
		Management of bleeding tendency
		Type Ib:
		• Granulocyte and granulocyte-macrophage colony-stimulating factors to correct neutropenia

Table 21.5 Clinical features of the glycogen storage diseases (*continued*)

	Clinical features	Treatment

Type III glycogen storage disease	Deficiency of glycogen debranching enzyme:
	• Impairs release of glucose from glycogen but does not affect glucose released from gluconeogenesis
	• Type IIIa involves both liver and muscle (most patients)
	• Type IIIb: only the liver is affected
	Clinical features:
	• Hepatomegaly
	• Growth retardation
	• Hypoglycaemia
	• Hyperlipidaemia
	• High liver transaminases
	• Fasting ketosis
	• Liver-related symptoms improve with age and disappear after puberty
	• Overt liver cirrhosis occurs rarely
	• Neuromuscular involvement, slowly progressive weakness and distal muscle wasting
	Liver histology:
	• Universal enlargement of hepatocytes by glycogen
	• Presence of fibrosis (non-progressive in most cases)
		Dietary management is less demanding than in type I:
		• Symptomatic if hypoglycaemia is present:
		  ○ Frequent meals high in carbohydrates with cornstarch supplements or
		  ○ Nocturnal gastric drip feedings
		• Diet high in protein during the daytime plus overnight protein enteral infusion may be of some benefit in patients with myopathy

Type IV glycogen storage disease	Branching enzyme deficiency:
	• Accumulation of glycogen with unbranched, long outer chains
	• Unbranched glycogen is significantly less soluble than normal glycogen
	Clinical features:
	• Progressive liver cirrhosis with portal hypertension and death often occurs before the age of 5 years (minority not progressive)
	• Typically presents in the first year of life
	• Hepatosplenomegaly
	• Failure to thrive
	• Hypoglycaemia is rare
	Histology:
	• Diffuse interstitial fibrosis
	• Wide fibrous septa
	• Abnormally large hepatocytes with stores of coarsely clumped material (glycogen and aggregations of amylopectin-like material)
		No specific treatment:
		• Maintenance of normoglycaemia and adequate nutrient intake:
		  ○ Improves liver function
		  ○ Improves muscle strength
		  ○ May extend the time for growth
		• Liver transplantation for progressive hepatic failure may be effective

Table 21.5 Clinical features of the glycogen storage diseases (*continued*)

	Clinical features	Treatment

Type VI glycogen storage disease	Deficiency in liver phosphorylase or defects in one of the four subunits of phosphorylase kinase:
	• Heterogeneous group of diseases
	• Phenotypes cannot easily be distinguished clinically
	Clinical features:
	• Relatively benign
	• Usually presenting with hepatomegaly and growth retardation in early childhood
	• Hypoglycaemia and hyperlipidaemia mild
	X-linked phosphorylasekinase deficiency most common:
	• Classical presentation at age 1–5 years:
	  ○ Protuberant abdomen due to hepatomegaly
	  ○ Fasting hyperketosis
	  ○ Mild elevation of cholesterol, triglycerides, AST and ALT
	• Clinical symptoms tend to disappear gradually with age
	• Most achieve normal final height
	Autosomal phosphorylase kinase deficiencies:
	• Early childhood
	• Hepatomegaly
	• Growth retardation
		Symptomatic
		• High-carbohydrate diet and frequent feedings for hypoglycaemia
		• Most patients require no specific treatment
		Prognosis is usually good
		Adult patients have minimal hepatomegaly and normal stature

Glycogen synthase deficiency	Different from other glycogen storage diseases:
	• Decreased glycogen stores
	• Present in early infancy
	  ○ Fasting hypoglycaemia
	  ○ Hyperketonaemia
	  ○ No hepatomegaly or hyperlipidaemia
	• Hyperglycaemia and a rise in blood lactate concentration may occur after meals (glucose is preferentially converted to lactate in the absence of glycogen synthesis)
	Glucagon effect:
	• During fasting, administration of glucagon has no effect on blood glucose, lactate or alanine concentrations
	After a meal, glucagon causes a rise in glucose and a fall in lactate and alanine
		Symptomatic:
		• Frequent feedings to alleviate hypoglycaemia
		• Protein-containing preferred to meals rich in carbohydrate:
		  ○ Glycogen synthesis is compromised and excess glucose is converted to lactate

disruption of the normal mechanisms of glycogenolysis and gluconeogenesis (Table 21.5). Treatment focuses on avoiding hypoglycaemia and managing the hepatic and extrahepatic consequences of these diseases.

Biliary atresia

Biliary atresia is a very rare congenital condition of unknown cause in which there is obliteration or discontinuity of the extrahepatic biliary system. It is the most common surgically treatable cause of cholestasis encountered during the newborn period. The incidence is highest in Asian populations.

Clinical features

Biliary atresia is indistinguishable from other causes of neonatal jaundice. As well as jaundice, patients may exhibit pale stools, dark urine, failure to thrive, splenomegaly and hepatomegaly. In any neonate with prolonged jaundice that is resistant to phototherapy and/or exchange transfusions, a search for secondary causes should ensue. Kernicterus does not develop as the liver is still able to conjugate bilirubin, which is unable to cross the blood–brain barrier

Biliary atresia is divided into two distinct groups:

- Isolated biliary atresia (postnatal form), which accounts for 65–90% of cases;
- Associated situs inversus or polysplenia/asplenia with or without other congenital anomalies (fetal/embryonic form), comprising 10–35% of cases.

In addition there are three distinct types of atresia (Box 21.2).

Box 21.2 Types of biliary atresia.

- Type I involves obliteration of the common duct; the proximal ducts are patent
- Type II is characterised by atresia of the hepatic duct, with cystic structures found in the porta hepatis
- Type III (>90% of patients) involves atresia of the right and left hepatic ducts to the level of the porta hepatis

Investigations

- **Mandatory**:
  - Blood tests show marked conjugated hyperbilirubinaemia;
  - Ultrasound investigation or other forms of imaging can confirm the diagnosis.
- **Further testing**:
  - Radioisotope scans of the liver;
  - Liver biopsy.

Management

If the intrahepatic biliary tree is unaffected, surgical reconstruction of the extrahepatic biliary tract (hepatoportoenterostomy) is possible (Kasai procedure). If the atresia is complete, liver transplantation is the only option. A third of patients will have inadequate bile flow following the Kasai procedure and will require liver transplantation.

Postoperative breastfeeding is encouraged when possible because breast milk contains both lipases and bile salts to aid in lipid hydrolysis and micelle formation. Theoretically, breast milk may also protect against cholangitis.

22

Viral hepatitides

Hepatitis A

Hepatitis A virus (Table 22.1) is highly infectious and spread by the faeco-oral route. Development of cell-line virus culture techniques has led to the development of vaccines.

Epidemiology

Hepatitis A has a worldwide distribution with higher rates occurring in communities with low standards of sanitation. Outbreaks in industrialised countries have been seen to occur in daycare centres and in association with sewage-contaminated shellfish, in homosexual men and in IV drug abusers. There have been very rare reports of transmission by blood transfusion.

Pathogenesis

The hepatitis A virus (HAV) is very stable, withstanding substantial heat, drying, low pH and detergents. This means it is able to survive in the environment (including in foods and drinking water) and acid barrier of the stomach, and be excreted in the bile, leading to faecal shedding.

The mechanisms responsible for hepatocellular injury remain poorly characterised but appear to be caused by the host's response to infection rather than a direct cytopathic effect of the virus. The long incubation phase of the virus is related to its ability to interfere with normal mechanisms for the recognition of viral infection and resultant synthesis of interferon (IFN)-β. With the onset of hepatocellular injury, HLA-restricted, virus-specific, cytotoxic, CD8+ T cells begin to secrete IFN-γ, which stimulates the recruitment of additional, non-specific inflammatory cells, causing hepatocellular injury.

The secretion of neutralising antibodies occurs concurrent with the earliest evidence of serum aminotransferase elevation and hepatocellular injury. Neutralising antibody is of primary importance in protection against HAV infection and disease.

Clinical features

Following an incubation period of 15–50 days (average 28–30 days), symptomatic individuals develop an acute febrile illness with jaundice, anorexia, nausea, abdominal discomfort, malaise and dark urine. Viral shedding is extensive throughout the incubation phase and continues for a further 1–3 weeks in adults, longer in young children. Most infections in infants and preschool children are very mild or asymptomatic. Symptoms are more common in adults, up to 70% having some symptoms, and with the severity tending to increase with age. While fulminant hepatitis can develop, it is rare. Chronic carrier states do not occur and permanent hepatic damage is extremely unlikely. However, patients with chronic liver disease are at particular risk of exacerbation with HAV and should be protected from infection.

Investigations

Diagnosis relies on the detection of serum antibodies to HAV (Figure 22.1). Immunoglobulin M (IgM)-specific antibody indicates recent infection and develops 5–10 days after exposure and can persist for up to 6 months. Immunoglobulin G

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Table 22.1 Hepatitis viruses.

	A	B	C	D	E
Family	Picornavirus	Hepadnavirus	Flavavirus	Deltavirus	Calcivirus
Size (nm)	27	42	30–60	40	32
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Length (kb)	7.5	3.2	9.4	1.7	7.5
Transmission	Faeco-oral	Parenteral Sexual	Parenteral ?Sexual	Parenteral Sexual	Faeco-oral
Chronic infection (%)	None	3–7	80–90	2–70	None
Markers of infection	HAV RNA	HBsAg HBeAg	HCV RNA	HDV RNA	HEV PCR

ss, Single stranded; ds, double stranded.

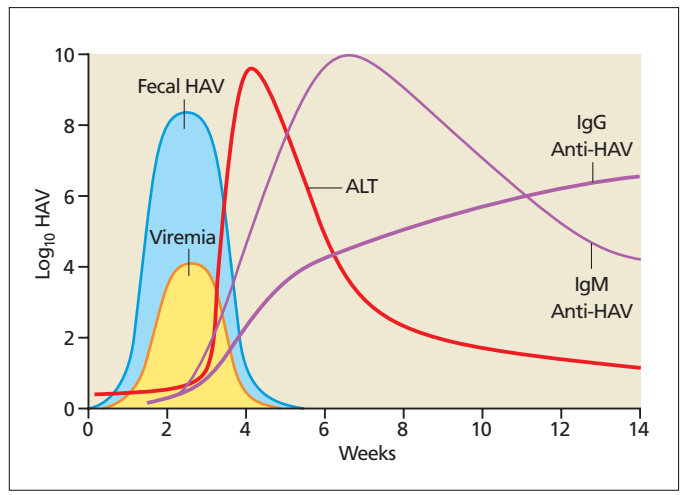

Figure 22.1 Natural history of hepatitis A.

(IgG) antibody is detectable shortly after the appearance of IgM. Virus culture is not used in routine diagnosis.

Management

- Management of the infected patient is largely symptomatic.
- Vaccination is effective both in preventing infection and disease:
  - There is an ongoing role for the use of immunoglobulin in the control of outbreaks of the disease as long as it is given within 2 weeks of contact with the disease. Protection against HAV was first achieved using human normal IgG, providing passive immunity to the virus;
  - Use of immunoglobulin for vaccination has largely been replaced by the use of inactivated hepatitis A vaccines.
- While universal and targeted programmes for childhood immunisation have been introduced in the USA and Australia, in most industrialised

countries vaccination is recommended only for groups at high risk of infection or in whom infection is more likely to cause serious illness. These groups include:

- Patients infected with hepatitis B and C;
- Travellers to countries with high rates of hepatitis A;
- Certain occupational groups:
  - Employees of early childhood services;
  - Those involved in the care of the intellectually disabled;
  - Healthcare workers exposed to faeces;
  - Sewerage and other workers exposed to faeces;
  - Military personnel.
- Men who have sex with men;
- Injecting drug users;
- Recipients of blood products such as factor VIII.

Special attention should be paid to the group chronically infected with other hepatitis viruses as superinfection with HAV in this group leads to increased morbidity and mortality. All patients should receive hepatitis A vaccine before liver decompensation occurs and, if this has not occurred prior to consideration for transplantation, as early as possible before liver transplantation.

Hepatitis B

This hepatotropic DNA virus can cause chronic infection, causing chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) (Table 22.1).

Epidemiology

Hepatitis B virus (HBV) infection is one of the most common infections worldwide with 400 million people estimated to be carriers. The mortality rate associated with HCC and other terminal complications of HBV infection is approximately one million people per year.

The *risk factors* for HBV infection include:

- Transfusion;
- Needle sharing;
- Sexual transmission;
- Perinatal transmission;
- Men who have sex with men;
- Promiscuous heterosexuals;
- Immunosuppressed patients;
- Patients on haemodialysis;
- Transplantation;
- Healthccare transmission.

The prevalence of HBV infection varies widely and correlates with risk of infection, age of infection and mode of transmission (Table 22.2).

Eight genotypes are recognised (A–H). Each genotype:

- Is associated with a particular geographical prevalence.
- May also be of clinical importance:
  - Patients with genotype C infection develop advanced liver disease more frequently than B or D;
  - Rate of HBeAg seroconversion is lower in genotype C infection;
  - Genotype C infection is associated with risk of HCC.

Table 22.2 Epidemiology and modes of transmission of hepatitis B virus infection.

	High	Intermediate	Low
Carrier rate (%)	8	2–7	1
Geographical distribution	Southeast Asia China Pacific islands Sub-Saharan Africa Alaska (Eskimos)	Mediterranean basin Eastern Europe Central Asia Japan Latin and South America Middle East	United States and Canada Western Europe Australia New Zealand
Predominant age at infection	Perinatal and early childhood	Early childhood	Adult
Predominant mode of infection	Maternal–infant Percutaneous	Percutaneous Sexual	Sexual Percutaneous

Pathogenesis

The innate immune system does not appear to play a role in HBV disease pathogenesis or viral clearance. Instead:

- HBV remains undetected in the liver and continues to replicate non-cytopathically until the adaptive immune response is initiated;
- At the time of onset of hepatocellular damage, virus-specific CD4+ T helper cells are involved in facilitating the induction and maintenance of CD8+ cytotoxic T lymphocytes (which have a fundamental role in the pathogenesis of liver cell injury);
- This pathogen-specific response is supported by the influx of non-virus-specific inflammatory cells, including mononuclear and polymorphonuclear cells;
- Recent evidence also points to an important role for platelets in the modulation of liver damage.

Clinical features

The clinical manifestations of HBV vary greatly between the acute and chronic phases of the disease. In the *acute phase*, which occurs in the 6 months after infection, the majority of patients are asymptomatic or demonstrate only mild fatigue. In some cases, however, there may be subclinical or clinical icterus, or very infrequently fulminant hepatitis.

In the *chronic phase*, the clinical manifestations can range from asymptomatic liver test abnormalities to chronic hepatitis, cirrhosis and HCC. A number of factors determine whether an individual will clear an acute HBV infection or go on to develop chronic hepatitis.

- Age is the most important, with carrier rates of >90% in patients infected as a newborn but <5% in those infected as adults;
- Immunological status, with immunocompromised patients (HIV, renal failure, post-transplant patients) having high rates of chronicity;
- Severity of acute disease determines progression to chronicity: those with less severe acute illness mount a less effective immune response and so are less likely to clear viral replication.

The disease is divided into three phases:

1. Replicative, during which aminotransferases are largely normal and there is little liver damage;
2. Inflammatory, where the aminotransferases become elevated, liver biopsy shows chronic hepatitis and viral replication declines;
3. Patients may enter the inactive phase where viral replication has stopped, the aminotransferases normalise and there is no ongoing liver inflammation.

Investigations

- To make a *diagnosis* of chronic HBV infection, the hepatitis B surface antigen (HBsAg) must be positive for 6 months; however, in practice the diagnosis is often suspected before this.
- Other markers are used to determine *immunity* and *infectivity*:
  - Antibodies to HBsAg (anti-HBs) indicate immunity either following vaccination or clearance of an acute infection;
  - Positivity for the HBV E-antigen (HBeAg), in the presence of HBV-DNA, indicates active replication;
  - Level of HBV-DNA correlates with the amount of virus in the circulation and has prognostic implications;
  - IgM antibodies to the HBV core protein (IgM anti-HBc) suggest recent exposure, except that patients with reactivation of infection may also be IgM anti-HBc positive.

Two special situations relating to chronic HBV infection are described in Boxes 22.1 and 22.2.

Box 22.1 Predicting risk of cirrhosis and hepatocellular carcinoma.

Serum HBV DNA level is the strongest predictor of progression to cirrhosis and also contributes a dose-dependent effect on the risk of HCC. This risk is independent of ALT level and HBeAg status. Care must be taken in applying these results:

- More than one test is needed (as the level of HBV fluctuates greatly)
- In patients with perinatal or early childhood infection
- In those with a shorter duration of infection

Box 22.2 HBeAg-negative chronic hepatitis B.

In chronic HBV infection, loss of the HBeAg is usually associated with development of the anti-HBe antibody and transition from the phase of high HBV replication to an inactive phase of infection. However, a variable proportion of patients continues to have, or re-develop, high serum HBV-DNA levels. This is termed HBeAg-negative chronic HBV infection and is a potentially severe and progressive form of liver disease.

The first discovered causes for this transformation were mutations in the precore region of the viral DNA, preventing translation of the e antigen by the core region. It generally occurs in geographical areas where HBV infection is transmitted vertically or even horizontally in very early life, and where the B and D genotypes of HBV prevail. HBeAg-negative chronic HBV infection may also develop with precore wild-type HBV strains, and in association with mutations in the basic core promoter region of the viral DNA.

Definitive diagnosis requires sequencing of the precore region but this technique is confined to research settings. In practice the diagnosis is made by:

- HBsAg positive for at least 6 months
- Negative serum HBeAg and usually positive anti-HBe antibody for at least 6 months
- Increased serum ALT >2 × upper limit of normal (ULN) on one occasion or ALT >1.5 × ULN on at least 2 monthly determinations
- Detectable serum HBV DNA
- Exclusion of other causes of liver disease
- Moderate-to-severe necroinflammation on liver histology

Common non-HBV causes of liver damage in this setting include superinfections with hepatitis D or C viruses, alcohol excess, hepatotoxic drugs and rare metabolic diseases.

In HBeAg-negative chronic HBV infection, treatment responses to IFN and lamivudine have been disappointing, with frequent relapse at the end of treatment and higher rates of lamivudine resistance than in the treatment of wild-type virus strains.

Management

Prevention

Prevention is the cornerstone of management of HBV:

- Safe sex;
- Avoidance of sharing of IV drug use;
- Use of gloves;
- Careful cleaning of blood or body fluid spills;
- Disposal or adequate sterilisation of surgical instruments (including tattoo and piercing equipment);
- Careful disposal of sharps;
- Use of goggles where there is a risk of infected material splashing into the eye
- Immunisation.

Immunisation is safe and effective. Many countries with a high endemic incidence of HBV have a policy of universal childhood vaccination. Elsewhere vaccination is recommended for:

- Those exposed to blood or blood products;
- Travellers who plan to spend long periods in high prevalence areas or with pre-existing medical conditions that place them at a higher risk of requiring medical procedures abroad (including pregnancy);
- Haemophiliacs;
- Prisoners and prison officers.

All pregnant women should be screened for HBV and, if positive, the baby should receive vaccination soon after birth using an accelerated schedule.

Treatment

Current therapies for chronic HBV infection fall into two categories:

- IFN-α:
  - Used for a finite period with durable response in a subset of patients;
  - Disadvantages of administration by injection and adverse effects.
- Oral nucleoside and nucleotide analogues (e.g. lamivudine):

- Better tolerated but associated with resistance;
- Expensive given they require administration for lengthy periods.

In addition, assays, including genotyping, HBV-DNA levels, genomic analysis, precore and core promoter mutations, and resistance mutations can be used to guide therapy. The overriding principle of therapy is that early, profound, sustained viral suppression improves response rates and reduces resistance.

Hepatitis D

Hepatitis D virus (HDV) is a subviral agent, dependent for its life cycle on HBV (Table 22.1). Co-infection or superinfection with this agent in HBV complicates the course of the disease.

Epidemiology

It is estimated that 20 million of the more than 400 million chronic HBV carriers worldwide also have chronic HDV. As both HBV and HDV are blood-borne, they share the same risk factors and may be contracted with the same or separate, exposures. When a naïve individual receives both viruses, it is referred to as *co-infection*, whereas *superinfection* is when a person chronically infected with HBV then contracts HDV.

Pathogenesis

In humans, HDV cannot replicate without the presence of HBV as it must make use of the three HBV envelope proteins. HBV particle assembly is very inefficient and most of the assembled particles are empty and do not contain the HBV nucleocapsid structure or genome. HDV assembly makes use of this excess production of envelope proteins, inserting the HDV genomic RNAs and other proteins into these empty particles.

Little information exists as to the exact mechanisms by which HDV enhances liver injury in HBV, however, it appears HDV replication itself is not cytopathic; instead immune mechanisms (both humoral and cellular) may be involved in the pathogenesis of liver injury.

Clinical features

Acute HDV superinfections carry a much greater risk of fulminating hepatitis and resultant liver failure than HBV alone. Chronic HDV infection is associated with more rapidly progressing liver damage.

Investigations (Figure 22.2)

The diagnosis of HDV should be considered in all patients diagnosed with HBV. It is particularly important to consider superinfection in patients with HBV undergoing a flare in disease activity.

- HDV produces two proteins, the small and large delta antigens (HDAg-S and HDAg-L). Even though these antigens are 90% identical they have different effects in infection:
  - HDAg-S is produced early and is required for viral replication;
  - HDAg-L is produced later and is an inhibitor of viral replication but is required for viral particle assembly.
- Total anti-HDV antibodies are used to make the diagnosis of infection.
- Reverse transcriptase-polymerase chain reaction (RT-PCR) is used to measure HDV RNA for monitoring chronic infection.

HDAg, IgM anti-HD antibodies and IgG anti-HD antibodies all disappear within months after clearance of viral replication, but persist in chronic infection.

Management

Vaccination against HBV also protects against HDV, and there has been a worldwide decrease in the incidence of HBV superinfection with the initiation of HBV vaccination programmes.

Antivirals, such as lamivudine, do not reduce HDV titres.

Treatment of disease is limited to:

- Extensive IFN-α therapy; or
- In severe situations, liver transplantation.

Hepatitis C

Hepatitis C virus (HCV) is the most common of the chronic blood-borne infections (Table 22.1). It is estimated that as many as 170 million people are infected worldwide. It has six genotypes, the relative preponderance of which varies globally.

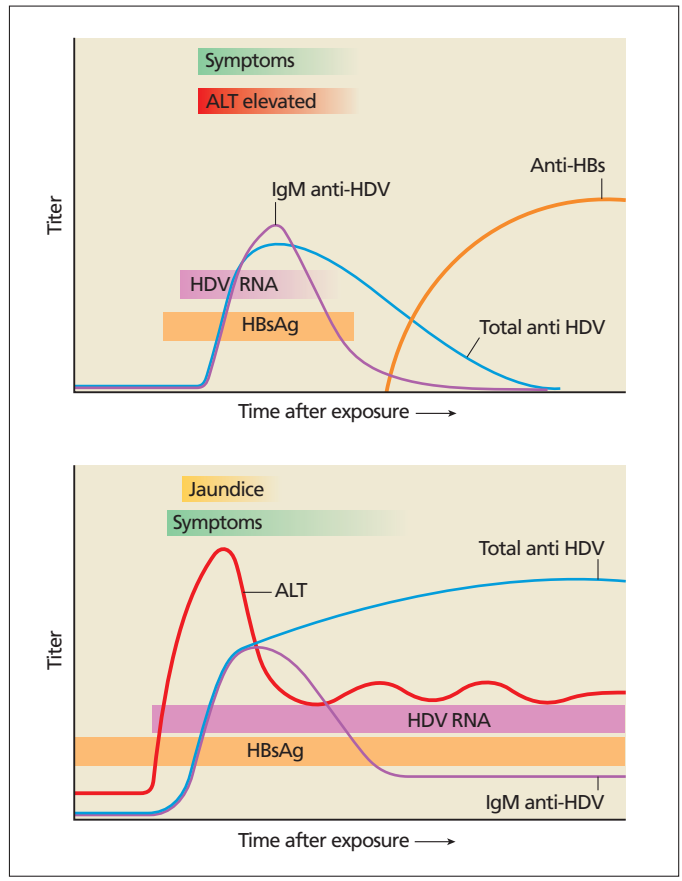

Figure 22.2 Serological and clinical course of hepatitis D co-infection (upper panel) and superinfection (lower panel).

Epidemiology

The risk factors for this blood-borne infection include:

- Blood transfusions (prior to institution of screening);
- IV drug use, tattoos, ear or body piercing;
- Sexual promiscuity;
- An HCV-positive partner;
- Incarceration.

Co-infection with HIV is common and the rate of HCV is high amongst the population with HIV. HCV has become one of the most important causes of morbidity and mortality in patients with HIV in the developed world.

Pathogenesis

Research into the mechanisms for liver damage in HCV infection has been greatly hampered by the lack of cell-line and animal models of disease. What is clear is:

- Innate immune system, the body's first line of defence, is insufficient to eliminate the virus;
- Acquired immune system is also attenuated, with T-cell failure, dysfunction and exhaustion;
- Hepatocyte apoptosis (programmed cell death) is enhanced, and this correlates with liver pathology and may contribute to fibrogenesis.

Clinical features

Acute infection is defined as the first 6 months following initial infection:

- Asymptomatic (the vast majority);
- Mild, non-specific complaints (fatigue, abdominal pain, anorexia, itching, and flu-like symptoms), which lead to a diagnosis only in a minority.

Chronic infection is defined as >6 months of documented infection:

- Frequently remains asymptomatic until late in the disease when liver fibrosis develops;
- Those symptoms that are experienced are non-specific and varying;
- Liver function tests are variably elevated and fluctuant.
- Extrahepatic manifestations occur more commonly with chronic HCV infection than other forms of chronic hepatitis and include:
  - Cryoglobulinaemia;
  - Porphyria cutanea tarda;
  - Thyroiditis;
  - Sicca syndrome;
  - Thrombocytopenia;
  - lLchen planus;
  - Diabetes mellitus;
  - B-cell lymphoproliferative disorders;
  - Membranoproliferative glomerulonephritis.

75% of patients with acute infection go on to become chronically infected. The risk of cirrhosis is approximately 1% per year, so at 20 years 20% will have cirrhosis and in that time 5% will develop HCC.

Investigations

Given the absence of specific symptoms, the diagnosis of HCV infection needs to be actively considered by the clinician. The diagnosis is often made incidentally with the discovery of elevated liver tests and is occasionally diagnosed at screening, such as occurs with blood donation or contact tracing.

- Anti-HCV antibodies:
  - Pros:
    - Positive in 80% within 3 months of infection, >90% within 5 months and >97% by 6 months;
    - Have a strong positive predictive value.
  - Cons:
    - Cannot determine ongoing infection;
    - May miss patients who have not yet developed antibodies or the rare patient who does not produce antibodies.
- RNA testing is necessary when antibody tests are negative, but the clinical suspicion is high. Virus is detectable in serum 1–3 weeks after infection:
  - Most common modality is PCR;
  - Titre assists in determining the probability of response to treatment but not severity or likelihood of progression.

Management

Prevention

Prevention of hepatitis C centres around education and programmes to eliminate the risk factors for HCV infection, in particular avoidance of the sharing of IV needles during elicit drug use. Because of the variability and high rate of mutation of HCV, as well as difficulties with animal and cell-line models of disease, it has not been possible to develop an effective vaccine.

Treatment

The primary goal is viral eradication. This is defined by the sustained virological response (SVR), which is the absence of detectable serum HCV RNA 6 months following the completion of therapy. Combination therapy is usual:

- Pegylated IFN-α, which gives increased and sustained duration of activity due to longer serum half-lifethan conventional IFN-α;
- Ribavirin, the nucleoside antimetabolite.

Monitoring of serum RNA levels can allow rationalisation of treatment. Viral genotype is the greatest predictor of treatment response.

- **Genotype 1**: SVR is achievable in nearly half of patients:
  - Lack of early viral response (EVR: defined as a minimum 2-log10 decrease in viral load during the first 12 weeks of therapy) is a strong predictor of not achieving SVR, enabling early treatment discontinuation;
  - However, treatment of the (rarely diagnosed) acute infection is warranted, resulting in a >90% success rate with half the treatment time required for chronic infections.
- **Genotypes 2 and 3**: SVR is achievable in 80%:

- Often need lower doses of ribavirin and a shorter treatment duration than genotype 1.

There are significant adverse effects associated with the use of IFN-α and PEG-IFNs, including fatigue, flu-like symptoms, GI disturbances, haematological abnormalities, neuropsychiatric effects (particularly depression), thyroid dysfunction and dermatological effects, such as alopecia and pruritus. In addition, ribavirin is associated with haemolytic anaemia. Because treatment success is directly related to adherence to treatment, dose reductions and discontinuations should be avoided if possible, hence monitoring for, and management of, adverse effects is essential. Serotonin-reuptake inhibitors (SSRIs) are safe and effective for IFN-associated depression. Anaemia caused by ribavirin can be treated using erythropoietin.

Hepatitis E

Hepatitis E virus (HEV) is a distinct agent, unrelated to HAV, which causes epidemics of largely waterborne, enterically transmitted, acute hepatitis (Table 22.1).

Epidemiology

The first extensively studied epidemic of HEV infection was in Delhi from 1955 to 1956. There were >29 000 icteric cases, with attack rates of 1–15% and an excess of cases among the 15–40 year olds. Studies of other epidemics in Asia and the Indian subcontinent have since shown a high susceptibility in children also and a case-fatality between 0.2% and 4%. In addition, there is a high risk of unexplained fulminant liver failure in pregnant women who are infected, especially in the third trimester. Intrauterine infection is common and associated with substantial prenatal morbidity and mortality. Outbreaks have been especially documented in countries of South-East Asia and Northern Africa.

Transmission:

- Primarily faeco-oral;
- Food-borne HEV infections increasingly detected;
- Vertical transmission in HEV-infected pregnant women is up to 50%;
- Parenteral transmission seems to be low;
- No evidence for sexual transmission.

Viraemia is usually brief, except in the immunosuppressed (e.g. after renal transplants), where it can be protracted. It appears that HEV can cause zoonotic infection and other mammalian hosts may constitute important reservoirs for the disease in humans.

Pathogenesis

HEV is the prototype member of the Hepevirus genus, family Hepeviridae. The virus was identified for the first time by immunoelectron micrograph in the faeces of an infected human. It has a spherical and non-enveloped virion, with surface spikes as well as cup-like indentations.

While an oral route of infection has been clearly demonstrated, the site of primary replication has not been identified, but is likely to be in the intestinal tract. The virus reaches the liver, presumably via the portal vein, and replicates in the cytoplasm of hepatocytes. It is able to survive the range of pH as it transits through the GI tract. While man is the natural host, it seems very likely animals serve as a reservoir with several claims of infection in domestic sheep and swine. Zoonotic transmission of HEV has also been demonstrated from deer to humans.

Clinical features

HEV infections manifests as epidemics of sporadic hepatitis in disease-endemic areas following an incubation period of 15–60 days (mean 40 days). As with other viral hepatitides a spectrum of symptoms occurs:

- Asymptomatic (probably far more common than icteric disease);
- Acute viral febrile illness without any characteristic features. When infection is symptomatic it produces an acute self-limiting hepatitis, which runs a course of a few weeks. However, in some patients there may be a prolonged cholestatic course.

Symptomatic disease can be divided into two phases:

- **Pre-icteric phase**, lasting 1–10 days (average 3–4 days) with GI symptoms (epigastric pain, nausea and vomiting);
- **Icteric phase**, beginning abruptly with jaundice, dark urine and clay-coloured stools. Two-thirds of patients also report arthralgia. There is a:

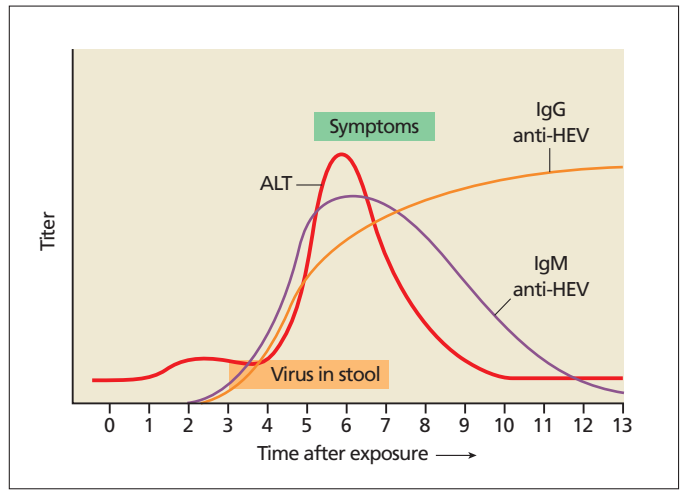

Figure 22.3 Serological and clinical course of hepatitis E virus infection.

- Variable rise in serum bilirubin (predominately conjugated);
- Marked elevation in aminotransferases that precedes symptoms by as long as 10 days and peaks at the end of the first week (degree of transaminase elevation does not correlate with disease severity).

An uncomplicated infection lasts 12–15 days with complete recovery within 1 month. Superinfection in chronic liver disease causes severe liver decompensation, a protracted course, and high morbidity and mortality. Chronicity of infection has not been documented apart from in cases with immunodeficiency.

Investigations (Figure 22.3)

- HEV RNA in stool can be detected in the pre-icteric phase, and then declines, disappearing by peak of ALT.
- Anti-HEV IgM in serum identified at onset of symptoms, detectable for 2 weeks to 3 months.
- Anti-HEV IgG increases promptly after IgM, persisting for up to several years in 50% of patients.

Enzyme immunoassays (EIA) and immunochromatography are the most convenient detection methods. In residents of, or travellers to, endemic areas, testing for HEV infection should be included in the first line of diagnostic work-up for acute hepatitis.

Management

While vaccine development and testing is ongoing there is, as yet, no effective vaccine available. HEV infection control and prevention strategies aim at improving hygiene conditions in endemic areas and detecting contaminated sources. Improving sanitation and providing clean drinking water and proper sewage disposal can reduce infections.

Other viral hepatitides

A number of other viruses can cause acute, and less commonly chronic, hepatitis:

- Epstein–Barr virus (EBV; the commonest);
- Cytomegalovirus (CMV);
- Varicella zoster virus;
- Herpes simplex virus.

Epstein–Barr virus hepatitis

Epidemiology

Almost 95% of the population is seropositive for EBV infection by the end of childhood. Most infections are completely asymptomatic in childhood, but symptomatic disease tends to occur in adolescents and adults. It is more common in developed

Box 22.3 Epstein–Barr virus tests.

To diagnose infectious mononucleosis (IM), lymphocytes should represent >50% of leucocytes, 20% should be atypical and there should be positive serology. There are two types of serological test for EBV:

- Heterophil antibody tests
- Tests for antibodies to viral antigens

The *heterophil antibody tests*, Paul–Bunnel test and Monospot test (if done on slides), detect antibodies that cause agglutination of the red blood cells from another species. False-negative results are more common in those under 14 years (especially under 5). Positive heterophil antibodies are seen during the first month of illness and decrease rapidly after week 4, but last >6 months after onset of infection.

Antibodies to several antigen complexes may be measured, including the early antigen, EBV nuclear antigen (EBNA) and viral capsid antigen (differentiation of IgG and IgM subclasses of this is often used). Interpretation of these results can be somewhat complex. The antibody profiles seen in each of the main clinical situations are:

- *Susceptibility to EBV infection*: if antibodies to the viral capsid antigen are not detected the patient is susceptible
- *Primary infection*:
  - IgM antibody to the viral capsid antigen is present and antibody to EBNA is absent, or
  - Elevated IgG antibody to the viral capsid antigen and negative antibody to EBNA after at least 4 weeks of illness, or
  - Elevated antibody to early antigen
- *Past infection*: if antibodies to both the viral capsid antigen and EBNA are present, then past infection (from >4 months earlier) is indicated. Since 95% of adults have been infected with EBV, most will show antibodies to EBV from infection years earlier. High or elevated antibody levels may be present for years and are not diagnostic of recent infection
- *Reactivation*: if antibodies to EBNA are present, an elevation of antibodies to early antigen suggests reactivation. However, positive antibody to the early antigen test does not automatically indicate that a patient's current medical condition is caused by EBV; healthy people with no symptoms can have antibodies to the EBV early antigen for years after their initial EBV infection. Reactivation often occurs subclinically
- *Chronic EBV infection*: reliable laboratory evidence for continued active EBV infection is rare in patients who have been ill for >4 months. When the illness lasts >6 months, it should be investigated to see if other causes of chronic ill health or fatigue are present

countries where the transmission rates during childhood are lower.

Pathogenesis

The exact mechanisms by which EBV causes liver damage remain unclear. It seems likely the host's immune reaction, rather than cytolytic effects of the virus, is responsible. The histology in EBV-induced hepatitis includes:

- Swelling and vacuolisation of the hepatocytes
- Periportal infiltration by lymphocytes and monocytes
- Mononuclear infiltration of the sinusoids
- Bile ducts are often mildly swollen but obstruction is rare

Clinical features

The term infectious mononucleosis describes the triad of:

- Fever;
- Sore throat;
- Adenopathy.

in combination with the finding of atypical mononuclear cells in the blood, as occurs with EBV infection.

Non-specific abdominal discomfort and nausea is seen in up to 15% of patients. Splenomegaly is detectable in up to 60%, but hepatomegaly in only about 15%. *Rare complications* include:

- Splenic rupture;

- Liver failure due to acute and/or chronic EBV infection (especially post-transplantation or in association with other immunodeficiency);
- Autoimmune hepatitis and HCC (controversially associated in Asian people);
- Lymphoproliferative disorders and lymphoma.

Investigations

Liver enzyme elevations are seen in 80–90% of those infected and are largely asymptomatic.

- Transaminases are elevated to two to three times the upper limit of normal. If elevations of >10 times are seen, it is less likely the diagnosis is EBV. The liver function abnormalities usually occur in the second week of illness and resolve within 2–6 weeks.
- Alkaline phosphatase is elevated in 60%.
- Bilirubin is elevated in 45% (but jaundice occurs in <5%) and is self-limited. Jaundice may be cholestatic or haemolytic and a FBC and peripheral blood film should be performed to detect haemolysis.

The *diagnosis* of EBV infection revolves around recognition of the typical clinical symptoms in association with positive EBV IgM antibody, monospot and/or heterophile antibody tests (see Box 22.3). False-positive monospot tests occur in HIV, endocarditis and acute hepatitis A. Polymerase reaction testing is necessary where the suspicion is high but serological tests are unremarkable. Other potential viral aetiologies must be considered.

Management

Treatment is supportive and the vast majority of cases resolve spontaneously. Steroids and antiviral medications have been used in severe disease but remain of unproven benefit. Patients with splenomegaly should be advised to avoid abdominal trauma and patients with elevated transaminases should avoid hepatotoxins until liver abnormalities resolve.

23

Drug-induced liver injury

Damage to the liver by medications is not uncommon and is the main reason for cessation of development of a drug or regulatory decisions to remove drugs from the market. In the majority of cases, drug-induced liver injury (DILI) is an unpredictable idiosyncratic reaction. However, there are important exceptions that cause DILI by dose-dependent mechanisms. Liver injury takes three forms: hepatocellular injury, cholestasis and mixed. Treatment relies on prompt diagnosis and removal of the offending drug.

Pathogenesis

Hepatocellular injury may result from the drug or its metabolites. Whilst most reactions are idiosyncratic, paracetamol and methotrexate are exceptions and cause direct hepatocellular toxicity. Idiosyncratic reactions may be either metabolic or immune mediated, or a combination of the two.

Given the variety of cellular mechanisms causing DILI, it cannot be viewed as a single disease. These mechanisms include:

- Disruption of the cell membrane;
- Production of immune targets by covalent binding of the drug to cell proteins;
- Inhibition of cellular pathways of drug metabolism;
- Abnormal bile flow due to disruption of subcellular actin filaments or interruption of transport pumps;
- Programmed cell death (apoptosis) mediated by tumour necrosis factor and Fas pathways;
- Inhibition of mitochondrial function causing accumulation of reactive oxygen species, lipid peroxidation, fat accumulation and cell death.

Pregnancy, concomitant medications and a history of drug reactions all increase susceptibility to DILI. The most important susceptibility factor is genetic variability. An example of this is differences in susceptibility related to polymorphisms in the *N*-acetyltransferase 2 gene which result in so-called fast and slow acetylators, the latter being at increased risk of isoniazid toxicity.

Clinical features

As DILI commonly simulates other common forms of acute and chronic liver disease, it is important that it is considered in every patient with liver dysfunction. The three commonest clinical scenarios (Table 23.1) are:

- Acute hepatitis;
- Cholestasis;
- A mixed condition resembling acute viral hepatitis.

The rarer forms are:

- Chronic hepatitis;
- Cirrhosis;
- Sinusoidal obstruction syndrome;
- Neoplasia.

Clues as to an allergic mechanism (fever, rash, peripheral eosinophilia) should not be overlooked. The time course may also help identify an allergic mechanism: typically there is a short latency period (1 month or less) and rapid symptom recurrence on rechallenge. In addition there may be haematological features including neutropaenia, thrombocytopaenia and haemolytic anaemia.

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Anton Emmanuel and Stephen Inns.

Table 23.1 Causes of drug-induced liver injury.

	Hepatocellular (elevated ALT)	Mixed	Cholestatic (elevated ALP and bilirubin)
Antimicrobials	Isoniazid Ketoconazole Pyrazinamide Rifampin Fluconazole Isoniazid Tetracyclines Highly active antiretroviral therapy Trovafloxacin	Clindamycin Nitrofurantoin Sulphonamides Trimethoprim-sulphamethoxazole	Amoxycillin-clavulanic acid Erythromycins Ciprofloxacin Fluconazole Rifampin
Psychiatric medicines	Buproprion Fluoxetine Paroxetine Risperidone Sertraline Trazodone	Amitryptilline Trazodone	Chlorpromazine Phenothiazines Tricyclic antidepressants Mirtazapine
Analgesics	Paracetamol NSAIDs		
Cardiovascular medicines	Amiodarone Methyldopa Statins/HMG-CoA reductase inhibitors Lisinopril Losartan	Captopril Enalapril Verapamil	Clopidogrel Irbesartan
Others	Valproic acid Methotrexate Acarbose Allopurinol Baclofen Herbal medicines (Ma Huang, Kava, pyrrolizidine alkaloids in comfrey, germander and chaparral leaf) Omeprazole	Azathioprine Carbamazepine Cyproheptadine Flutamide Phenobarbitol Phenytoin	Anabolic steroids Oral contraceptives Oestrogens Terbinafine

In rare cases, Steven–Johnson syndrome or toxic epidermal necrolysis strongly suggest an immunological mechanism.

In the case of hepatocellular injury the clinical features are non-specific and not always associated with jaundice. Prognosis is largely dependent on the presence of jaundice. and the rule of thumb is that the likelihood of mortality or liver transplantation is 10% in the presence of jaundice. Variables associated with a poor outcome include older age, female gender and AST levels.

Because the histological changes of DILI are not specific, the pattern of hepatotoxicity is defined by changes in the liver enzymes.

- Hepatocellular injury is defined by a rise in ALT > two-fold that of the upper limit of normal (2 × ULN) or an ALT/AP ratio ≥5.
- Acute cholestatic injury is defined by an increase in the ALP >2 × ULN or an ALT/ALP ≤2. Older age is associated with an increased likelihood of DILI being expressed as cholestatic damage. There are two subtypes:
  - Pure cholestasis (resulting in jaundice, itching and an increase in conjugated bilirubin, ALP and GGT, with minimal alterations in the transaminases; typically caused by anabolic or contraceptive steroids);

  - Acute cholestatic hepatitis (resulting in abdominal pain and fever, and a picture similar to acute biliary obstruction; typically caused by amoxicillin-clavulanate, macrolide antibiotics and phenothiazine neuroleptics, amongst many others).
- Mixed DILI is a clinical and biological intermediate, predominated by either hepatocellular or cholestatic features. It is defined by an ALT:ALP ratio between 2 and 5.

Investigations

Due to a lack of specific clinical and pathological features, the diagnosis of DILI is largely subjective and based on the temporal associations between the initiation of therapy and onset of symptoms, and the rate of improvement after cessation of therapy. Alternative diagnoses must be carefully excluded. Patients must be carefully questioned about the use of prescribed, over-the-counter and illicit drugs.

The latency period varies with each drug and is linked to the mechanism of damage. Intrinsic hepatotoxins may cause disease within a few hours; allergic reactions may have a latency of 1–5 weeks; and idiosyncratic reactions take between 1 and 12 weeks to manifest. With some drugs (amoxicillin-clavulanate, midecamycin, oxacin and trovafloxacin) there is a delay of 3 or 4 weeks between cessation of treatment and presentation. The reasons for this are unclear but might represent a late immune reaction due to retention of the drug in the body.

When patients are taking a number of medications, discerning the probable culprit can be very difficult. In the first instance, suspicion should be directed at the latest introduced drug and known hepatotoxins. The main causative agents in DILI are antibiotics, NSAIDs, antiseizure medications and herbal preparations.

Rapid improvements after withdrawal of the offending agent suggest a toxic aetiology:

- A decrease of 50% liver enzymes in the first 8 days following cessation is said to indicate that a hepatotoxic mechanism is 'highly likely'.
- Course is 'suggestive' of hepatotoxicity if the same improvement occurs within 30 days.
- The only way to confidently confirm idiosyncratic drug-induced hepatotoxicity is to demonstrate at least a doubling of the ALT (in hepatocellular toxicity) or ALP (in cholestatic injury) on rechallenge with the implicated drug. However, intentional rechallenge is contraindicated in hypersensitivity reactions due to the risk of a more severe reaction, and in idiosyncratic reactions the amount of drug needed to induce a reaction cannot be known. Hence, rechallenge cannot be used for purely diagnostic reasons and should only be attempted when continuation of the drug is essential.

Liver biopsy may be useful:

- Where there is a suspicion of an underlying liver disease;
- In the rare cases where there is chronic toxic hepatocellular injury;
- If the suspected offending agent needs to be continued for therapeutic reasons and hence it is important to quantify the degree of liver injury generated.

In hepatocellular DILI, the histology is variable with:

- Necrosis and inflammation, and often an abundance of eosinophils in the inflammatory infiltrate;
- Acute cholestasis causes hepatocyte cholestasis and dilated biliary canaliculi with bile plugs, but little or no inflammation and necrosis;
- Mixed injury often results in a granulomatous reaction seen on biopsy.

Management

Generally there is no effective treatment for DILI other than stopping the implicated drug and providing supportive care. The main exceptions are the use of *N*-acetylcysteine after paracetamol overdose and intravenous carnitine for valproate-induced mitochondrial.

Paracetamol overdose

In the UK paracetamol overdose is the commonest form of intentional self-harm, with 70 000 cases per year, and is the leading cause of acute liver failure. Serious or fatal adverse effects in adults occur at a dose of around 150 mg/kg.

Pathogenesis

Paracetamol is inactivated by liver conjugation to two metabolites: the glucoronide and the sulphate. It is then renally excreted. In overdose

conjugation is inundated and metabolism is by an alternative pathway, creating *N*-acetyl-p-benzoquinone imine (NABQI), which is then inactivated by glutathione. However, glutathione is easily run down, preventing inactivation of NABQI and resulting in reaction with nucleophilic aspects of the cell, causing necrosis of the liver and kidney tubules. Increased toxicity occurs with:

- Drug-induced induction of the cytochrome P450 system:
  - Rifampicin;
  - Carbamazepine;
  - Phenytoin.
- Low glutathione reserves due to:
  - Genetic variation;
  - HIV positivity;
  - Malnutrition;
  - Ethanol excess;
  - Liver disease.

Clinical features

Patients are generally asymptomatic in the first 24 h after ingestion or have non-specific abdominal symptoms (such as nausea and vomiting). Hepatic necrosis begins after 24 h, resulting in right upper quadrant pain, jaundice and elevated transaminases. Examination reveals little until acute liver failure ensues.

Investigations

- Paracetamol level sampled 4 h after ingestion (or at presentation if after this time or if ingestion was staggered), usually with a salicylate level. In the case of staggered overdose, the level cannot guide treatment and is used only to confirm ingestion.
- Baseline FBC, U&E, creatinine and LFTs.
- Prothombin time is the best indicator of severity of liver failure.
- Blood glucose is measured as hypoglycaemia is common.
- Arterial blood gas is analysed as acidosis can occur early.

Box 23.1 N-acetylcysteine (NAC).

- NAC has beneficial effects by a number of protective mechanisms:
  - Precursor for glutathione
  - Supplying thiols
  - Antioxidants effects
- Its protective effect is greatest within 12 h of ingestion
- Allergy occurs in <5% of patients:
  - Infusion rate should be slowed if reaction occurs
  - Pretreatment with IV hydrocortisone and chlorphenamine if known allergy to NAC
  - Methionine is an alternative, but absorption is unreliable and it must be given early

Management

- Charcoal:
  - If there has been significant overdose (150 mg/kg or 12 g, whichever is the smaller);
  - When ingestion is within 1 h of presentation or is unknown.
- Urine output and blood glucose are monitored hourly. U&E, LFTs and INR should be checked 12 hourly.
- 4-h paracetamol level guides therapy. Risk is assessed using a nomogram :
  - Patients at high risk (i.e. those at risk of enzyme induction or glutathione depletion) are assessed using the 'high-risk' threshold;
  - *N*-acetylcysteine (NAC) is given to patients (Box 23.1):
    - With levels above the treatment line;
    - Immediately at presentation if the overdose is >150 mg/kg (or 12 g in an adult) *or* the overdose is staggered *or* the patient presents >15 h after ingestion.
- When there is significant hepatotoxicity, early referral to a specialist unit must be considered (see Chapter 9).

24

Vascular liver diseases

Obstruction of the venous system of the liver causes a spectrum of disease ranging from acute hepatic failure to passive hepatic congestion. It can be divided into three categories:

- Veno-occlusive disease;
- Budd–Chiari syndrome;
- Congestive hepatopathy.

In addition, reduction of oxygen delivery to hepatocytes (by obstruction of the arterial system or systemic hypotension or hypoxia, with/without concomitant congestion, can cause profound hepatic dysfunction.

Embryology

The liver arises from a diverticulum on the ventral surface gut and gives off two solid buds of cells which grow into columns or cylinders, termed the hepatic cylinders. These then branch and anastomose to form a close meshwork. This network invades the vitelline and umbilical veins, and breaks up these vessels into a series of capillary-like vessels, termed sinusoids, which ramify in the meshes of the cellular network and ultimately form the venous capillaries of the liver.

Vascular anatomy of the liver

The vessels of the liver are: the hepatic artery, portal vein and hepatic veins. Blood running to the liver travels in the hepatic artery and portal vein. These ascend to the porta, between the layers of the lesser omentum, in combination with the bile duct. The bile duct lies to the right, the hepatic artery to the left and the portal vein behind and between the other two (Figure 24.1). The hepatic veins convey the blood away from the liver and are formed as the sublobular veins unite to form progressively larger conduits. The hepatic veins converge to form three large trunks draining into the inferior vena cava.

The substance of the liver is composed of lobules. Each lobule consists of a mass of hepatic cells, arranged in irregular radiating columns between which are the blood channels (sinusoids). These convey the blood from the circumference to the centre of the lobule, ending in the intralobular vein, which in turn empties into a sublobular vein. The portal vein and hepatic artery, after entering the liver at the porta, run through the portal canals and repeatedly branch, eventually giving interlobular branches, which form a plexus outside each lobule. All the blood carried to the liver by the portal vein and hepatic artery finds its way into the interlobular plexus. From this plexus, lobular branches enter the lobule and end in the network of sinusoids between the cells.

Budd–Chiari syndrome

Budd–Chiari syndrome (BCS) is an uncommon and potentially life-threatening condition caused by the obstruction of hepatic venous outflow at any level from the small hepatic veins to the junction of the inferior vena cava (IVC) with the right atrium. Its presentation is variable depending on the degree and rapidity of onset of obstruction.

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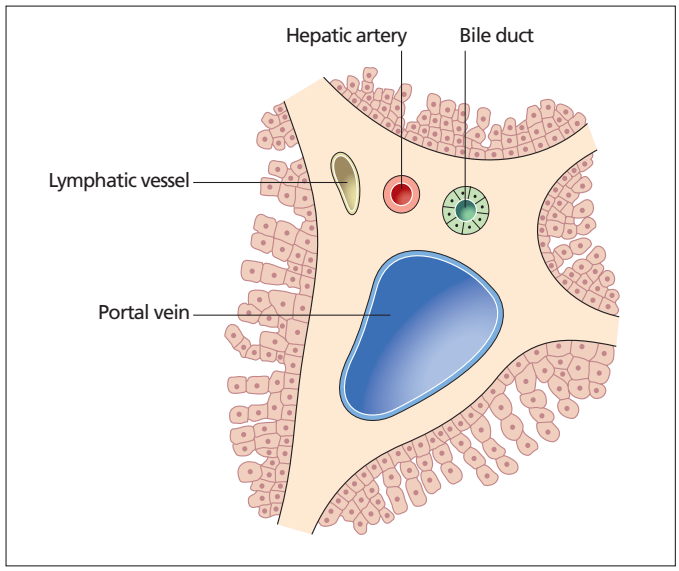

Figure 24.1 Cross-section of a portal canal.

Epidemiology and pathophysiology

BCS is an uncommon disorder which occurs in 1 in 100 000 of the general population worldwide. It is more common in women, and in the third or fourth decade. It has multiple aetiologies:

- Primary:
  - Intraluminal thrombosis (commonest cause):
    - Primary myeloproliferative disorders (especially polycythemia vera > essential thrombocythemia, myelofibrosis);
    - Inherited deficiencies of protein C, protein S and antithrombin III (factor V Leiden mutation underlies the majority of pregnancy- and oral contraceptive-related cases);
    - Paroxysmal nocturnal haemoglobinuria.
  - Vascular webs.
- Secondary:
  - To intraluminal invasion (by parasites or malignant tumour);
  - To extraluminal compression (by abscess, cyst or solid tumour).

The pathological features of BCS result from the increased sinusoidal pressure that occurs with hepatic venous obstruction. This in turn results in portal hypertension causing portal perfusion to decrease, potentially resulting in portal vein thrombosis (PVT; a complication which substantially worsens prognosis). Reduced venous perfusion and congestion result in hypoxic damage to the liver parenchymal cells, releasing free radicals. These cause oxidative injury to the hepatocytes and the development of centrilobular hepatocyte necrosis. Centrilobular fibrosis and nodular regenerative hyperplasia ensue and, ultimately, cirrhosis may occur. However, if sinusoidal pressure is reduced (by portosystemic shunt formation or the development of a portal venous collateral system), liver function improves.

Clinical features

BCS demonstrates a wide spectrum of clinical features, ranging from asymptomatic disease to fulminant liver failure, depending on the location, extent and rapidity of onset of the obstructive process, and whether there is portal vein occlusion. There is commonly ascites, hepatomegaly and abdominal pain. The disease can be classified into asymptomatic, fulminant, acute, subacute or chronic groups. However, the correlation between the history, duration of occlusion and prognosis is unclear (Table 24.1).

The natural history of BCS is poorly understood because most patients receive some form of treatment along the way. The introduction of anticoagulation and earlier recognition of asymptomatic disease has resulted in a decrease in mortality.

Table 24.1 Clinical features and classification of Budd–Chiari syndrome (BCS).

Clinical classification	Proportion of BCS	Presentation	Clinical features
Asymptomatic	5–20%	Incidental discovery of abnormal LFTs	Absence of symptoms due to large collaterals (intrahepatic and portosystemic) or the patency of one large hepatic vein
Acute	20%	Symptoms develop over a few weeks	Severe RUQ pain, hepatomegaly, jaundice and intractable ascites
Fulminant	Uncommon	Onset of encephalopathy within 8 weeks of symptom onset	Follows rapid complete occlusion of all major hepatic veins Acute-onset encephalopathy, renal failure, coagulopathy and marked aminotransferase elevations Acute development of oesophagogastric varices, tender hepatosplenomegaly
Subacute and chronic	>60%	Onset insidious over >6 months	Subacute: • Minimal ascites, with hepatosplenomegaly and vague RUQ discomfort • Jaundice absent or mild • Ascites and hepatic necrosis minimal (because hepatic sinusoids have been decompressed by a portal and hepatic vein collateral circulation) Chronic: • Presenting with complications of cirrhosis: variceal bleeding, encephalopathy, renal failure, coagulopathy, hepatopulmonary syndrome

Differential diagnosis

BCS is frequently misdiagnosed initially. Cholecystitis is considered due to the combination of abdominal pain and ultrasonographically visible thickening of the gallbladder wall. It is not unusual for these patients to come to cholecystectomy. BCS must be considered in any patient at risk of thrombophilia who presents with ascites, upper abdominal pain or abnormalities on LFTs.

IVC compression or thrombosis causes less severe disease, clinically recognisable by the development of leg oedema or venous collaterals over the trunk and back. It follows a chronic course, with repeated acute episodes eventually resulting in congestive cirrhosis. IVC obstruction is associated with good short-term prognosis but there is limited long-term data.

Cardiac conditions (tricuspid regurgitation, constrictive pericarditis, right atrial myxoma) can be ruled out by careful cardiovascular examination. The absence of a hepatojugular reflux on abdominal pressure rules out a cardiac cause of ascites.

Investigations

Diagnosis requires a high level of suspicion and should be considered in anyone presenting with ascites, hepatomegaly and right upper quadrant (RUQ) pain. Laboratory findings are non-specific. Ascitic albumin varies at different stages of the disease; however, the serum–ascitic fluid albumin gradient is high, usually with a total protein >25 g/l.

Diagnosis is dependent on *imaging*.

- Real-time or colour and pulsed Doppler ultrasound is the initial investigation of choice, with a sensitivity and specificity of nearly 85%. It can demonstrate hepatic vein obstruction or abnormal flow in large intrahepatic or subcapsular venous collaterals.
- Contrast-enhanced CT is less useful for visualisation of hepatic veins and the IVC;

however, it does allow assessment for parenchymal disease, ascites and splenomegaly.
- MRI with gadolinium enhancement allows excellent visualisation of the hepatic veins and IVC but, unlike Doppler, it does not demonstrate the direction of hepatic venous blood flow. It is most useful in cases where ultrasound is non-contributory but clinical suspicion is high.
- Venography is not essential for the diagnosis of BCS, but does give useful information about the extent of the thrombosis and the caval pressures. It guides decision-making when considering surgical treatment of BCS.

Pathology shows variable degrees of parenchymal damage dependent on the location and extent of venous congestion. Ischaemic necrosis and fibrosis in perivenular areas is characteristic. Concomitant PVT results in periportal fibrosis. In chronic BCS, collateralisation compensates for this and there may be caudate hypertrophic cirrhosis with atrophy in the rest of the liver.

Management

The goals of treatment are to:

- Alleviate obstruction;
- Prevent extension of thrombosis;
- Preserve hepatic function by decreasing centrilobular congestion.

Medical management

Medical therapy alone can only be considered when there is no ongoing hepatic necrosis (as indicated by the relative absence of symptoms, normal LFTs and easily controlled ascites). These patients should be carefully monitored for progression using serial upper GI endoscopies and liver biopsies. The focus is to:

- Control the ascites (low-sodium diet, diuretics or paracentesis with IV albumin cover);
- Prevent thrombosis extension (anticoagulation, or thrombolysis in the small number of cases where it is appropriate);
- Treat complications;
- Investigate and treat underlying cause.

Angiographic and surgical management

Restoration of hepatic blood flow may be achieved by the use of:

- Thrombolytic therapy:
  - Indicated in the acute situation where angiography suggests fresh thrombus;
  - Thrombolytic agent (urokinase or tissue plasminogen activator) can be given systemically or, preferably, directly into the obstructed hepatic vein.
- Percutaneous angioplasty:
  - To caval webs or short hepatic vein stenoses;
  - Excellent short-term patency, falling to 50% by 2 years;
  - Can be improved to 90% with use of intraluminal stents.
- Transjugular intrahepatic portosystemic shunt (TIPS):
  - Provides an alternative venous outflow tract to decompress the liver;
  - Useful as a bridge to liver transplantation and in acute situations, such as variceal bleeding and fulminant hepatic failure, where thrombolysis and angioplasty have been unsuccessful;
  - May function by allowing time for venous collaterals to form, so while long-term occlusion occurs in 50%, these patients do not generally worsen.
- Portosystemic shunt surgery:
  - Creates hepatofugal flow in the portal vein;
  - Recommended in subacute disease when the underlying cause has a favourable long-term outcome.

Liver transplantation

Liver transplantation is the treatment of choice in the presence of cirrhosis, fulminant hepatic failure or biochemical evidence of advanced liver dysfunction. The long-term survival after transplantation in BCS is 50–95%. While liver transplantation effectively cures most inherited thrombophilias, because of the frequent multifactorial aetiology of BCS, life-long anticoagulation is needed in most post-transplant patients.

Prognosis

5-year survival is 60% in patients with concomitant PVT and 85% in isolated BCS. Prognosis is associated with the presence of ascites, encephalopathy, prothrombin time and serum bilirubin levels. Histology on liver biopsy is *not* accurate in determining prognosis, perhaps because of the uneven distribution of hepatic lesions in BCS.

Hepatic veno-occlusive disease

Epidemiology and pathophysiology

Veno-occlusive disease (VOD) typically occurs after haematopoietic stem cell transplantation (HSCT), but also after ingestion of pyrrolizidine alkaloids. The reported incidence after HSCT varies from 5% to 50%, due to differences in chemotherapeutic regimens. The reported mortality of VOD varies greatly, between 3% and 67% depending on disease severity.

Pathophysiology

The histological features of VOD are:

- Loss of sinusoidal endothelial cell (SEC) fenestrae;
- Appearance of gaps in the SEC barrier;
- Narrowing of the sublobular and central veins due to subendothelial oedema;
- In advanced disease, the sinusoidal and venous lumena become obliterated.

One of the main hypotheses for the pathogenesis of VOD is that depletion of liver glutathione reserves diminishes the liver's ability to detoxify acrolein (which is an inactive but hepatotoxic metabolite of cyclophosphamide). It is unclear if coagulation plays a primary role or is a secondary event. It is also possible that immunological mechanism have a pathogenetic role.

Clinical features

Signs and symptoms develop within 3 weeks of exposure in the case of HSCT and are primarily those of tender hepatomegaly, fluid retention, ascites and jaundice. Liver enzyme changes may occur a few days later (hyperbilirubinaemia, sometimes in association with increased ALT and ALP).

In the majority, the first, and often only, symptom is RUQ pain.

Risk factors for the development of VOD include:

- Advanced age.
- Presence of liver injury prior to HSCT.
- Previous HSCT.
- Clotting cascade mutations (Factor V Leiden and prothrombin G20210A)
- Type and dose of the conditioning regimens prior to and during HSCT:
  - Cyclophosphamide is used in combination with busulphan;
  - Total body irradiation;
  - Carmustine and etoposide.

Investigations

- Liver biopsy is the diagnostic gold standard for VOD:
  - However, patients are frequently thrombocytopenic, making biopsy risky even when taken by percutaneous, laparoscopic or transvenous (transjugular or femoral) means;
  - Thus the diagnosis is primarily clinical. The Seattle and Baltimore clinical criteria are commonly applied and correlate well with biopsy-proven diagnosis;
  - Transvenous biopsy also allows measurement of the wedge hepatic venous pressures, providing useful additional diagnostic information.
- Ultrasound is useful primarily for excluding other disorders.
- Plasma plasminogen activator inhibitor-1 (PAI-1) levels have proven 100% sensitive and specific for VOD diagnosis in the group of post-HSCT patients with bilirubin levels 60 µmol/l (>3 mg/dl).

Important differential diagnoses for liver dysfunction post HSCT include:

- Acute graft-*versus*-host disease (GVHD):
  - Tends to occur later and only after intestinal and cutaneous manifestations become obvious;
  - Does not cause hepatomegaly or ascites.
- Sepsis-related cholestasis:
  - Does not cause hepatomegaly or ascites.
- Cyclosporin-induced cholestasis.

Management

Prevention

As there is no established effective therapy, prevention of VOD is the priority. This includes modifying the conditioning regimen in patients at increased risk of VOD and (possibly) use of ursodeoxycholic acid as prophylaxis. Heparin infusion may be useful but carries an increased risk of bleeding. Low-molecular-weight heparin is safer

and easier, and may have a preventive role but evidence is lacking.

Treatment

Once VOD is established, the treatment for most patients is simply diuretics and sodium restriction. Repeated paracenteses may be required. Hepatotoxic drugs should be avoided and infections treated promptly. Perhaps the most promising new development is defibrotide, a polydisperse oligonucleotide derived from porcine intestinal mucosa with antithrombotic and protective properties on the microvasculature but minimal haemorrhagic risk. Orthotopic liver transplantation is a possible last resort but is difficult and high risk in patients undergoing HSCT.

Portal vein thrombosis

Epidemiology and pathophysiology

The exact frequency of PVT is unknown. It occurs most commonly as a complication of cirrhosis, particularly in decompensated disease, and in up to 35% of cirrhotic patients with hepatocellular carcinoma (HCC). The combination of multiple aetiological factors is important in the pathogenesis (Box 24.1), a cause being identifiable in most cases, classifiable as general thrombophilic factors (60% of cases) and local factors (in 40%). These include systemic factors such as inherited prothrombotic disorders, acquired haematological diseases and sepsis, in particular *Bacteroides fragilis* infection.

PVT can be divided into four anatomical categories:

- Thrombus confined to the portal vein beyond confluence with the superior mesenteric vein (SMV);
- Extension into the SMV but patent mesenteric vessels;
- Diffuse splanchnic venous involvement with large collaterals;
- Splanchnic involvement but extensive fine collaterals.

This system is most useful in determining operability, but may also be helpful in determining prognosis, as thrombus involving the SMV is associated with a higher risk of bowel infarction and a lower risk of variceal bleeding than isolated PVT.

Box 24.1 Causes of portal vein thrombosis.

Idiopathic causes

Causes secondary to tumour

- Hepatocellular carcinoma
- Cholangiocarcinoma
- Pancreatic carcinoma
- Gastric carcinoma

Trauma

Intra-abdominal sepsis/inflammation

- Perinatal omphalitis
- Appendicitis
- Diverticulitis
- Ascending cholangitis
- Intra-abdominal abscess
- Pancreatitis

Haematological disorders

- Myeloproliferative disorders
- Clotting disorders (hypercoagulable syndromes)

Iatrogenic

- Umbilical vein catheterization
- Oestrogen therapy

Severe dehydration

Cirrhosis

Portal hypertension

'Portal cavernoma' formation or 'cavernous transformation of the portal vein' results from the development of multiple small vessels in and around the recanalising or occluded main portal vein, giving a leash of fine or markedly enlarged serpiginous vessels in place of the portal vein.

Clinical features

While somewhat arbitrary and often difficult, it is useful to distinguish between acute and chronic PVT. *Acute* onset is suggested by the absence of clinical, endoscopic and radiological evidence of portal hypertension, typically thrombosis occurring <60 days prior to assessment. *Chronic* thrombosis presents with the complications of portal hypertension, including GI bleeding, splenomegaly and hypersplenism. Ascites is rare, except in the elderly, unless there is comorbid liver disease. While the causes of acute and chronic PVT are similar, sepsis is a more common cause of chronic thrombosis.

The natural history of PVT is uncertain and reported mortality varies from 0–76%. Variceal bleeding is the presenting problem in approximately 30% of cases and is the most common complication of PVT. Concomitant disease, in particular bowel infarction, contributes greatly to the prognosis and is a more important cause of death than variceal bleeding.

Problems in the extrahepatic biliary tree are frequently seen, the mechanisms for which include biliary compression by choledochal or periportal varices, external compression by portal cavernoma formation, pericholedochal fibrosis or ischaemic stricturing. In addition, jaundice, cholangitis, choledocholithiasis, cholecystitis and haemobilia due to rupture of choledochal varices can occur.

Investigations

- Initial investigation of choice is colour Doppler ultrasound.
- Contrast-enhanced CT scanning is particularly useful for demonstrating portosystemic collaterals or the development of a cavernoma, which suggest well-established PVT.
- Where an underlying local cause is found, investigation for other co-factors is not required. However, where no local cause is found, systemic causes, including myeloproliferative disorders and prothrombotic conditions, should be sought.

Management

Treatment aims to either reverse or prevent the advancement of thrombosis and to treat the complications. Treatment recommendations are hampered by a lack of randomised controlled studies. Variceal bleeding is managed in standard fashion: endoscopic therapy and/or medical therapy, including non-selective beta-blockers and nitrates.

In PVT thrombolysis and/or anticoagulation may result in recanalization of the thrombosed portal system. Thrombolysis should be considered in acute PVT and anticoagulation considered for chronic thrombosis where there is no evidence of cirrhosis. No consensus exists as to the duration or degree of anticoagulation and generally a similar strategy to deep vein thromboses in the lower limb is applied: a finite course of treatment where a reversible cause is found but long-term anticoagulation where the underlying cause is not reversible.

Where splenomegaly causes hypersplenism, splenectomy may be of benefit. Symptomatic bile duct abnormalities are best treated endoscopically.

Congestive hepatopathy and cardiac cirrhosis

Epidemiology and pathophysiology

While mild degrees of hepatic dysfunction in the presence of congestive cardiac failure are common, the development of cardiac cirrhosis is rare. When it does occur, the chief causes are:

- Ischaemic heart disease (31%);
- Cardiomyopathy (23%);
- Valvular heart disease (23%);
- Restrictive lung disease (15%);
- Pericardial disease (8%).

The classical pathological description is that of ‘nutmeg liver’, with contrasting areas of red caused by *sinusoidal congestion* and bleeding in the *necrotic* regions surrounding the enlarged hepatic veins, and yellow due to the normal or *fatty liver* tissue. These macroscopic changes are also evident histologically. The degree of cholestasis is variable with occasional bile thrombi in the canaliculi. In the presence of chronic heart failure, *fibrosis* develops in the perivenular region, leading ultimately to bridging fibrosis between central veins. Cardiac fibrosis is distinct from primary liver cirrhosis in which fibrous bands tend to link adjacent portal areas. If the underlying cardiac disease is treated successfully, the early histological changes resolve, and even fibrosis may regress.

The pathogenesis of these changes relates to the reaction of the hepatic stroma evoked by increased venous pressure, hypoxia or hepatocellular necrosis. Thrombosis in the hepatic and portal veins is also contributory.

Clinical features

- Liver dysfunction in congestive cardiac failure is generally mild and asymptomatic, and is usually detected incidentally.
- With more severe congestion, mild jaundice, RUQ discomfort (due to stretching of the liver capsule) and ascites develop.

- Where severe jaundice and elevated aminotransferases develop, it is due to acute hepatic ischaemia resulting from marked reductions in cardiac output.
- Reported cases of fulminant hepatic failure have resulted from the combination of both hepatic congestion and ischaemia.

Symptoms of exertional dyspnoea, orthopnoea and angina may help in diagnosis. Examination may reveal tender hepatomegaly with a firm and smooth liver edge. Splenomegaly is uncommon and when it occurs, like ascites, is due to increased transmitted central venous pressure. The detection of jugular venous distension and hepatojugular reflux are helpful pointers to an underlying cardiac cause. The liver may be pulsatile, particularly in the presence of tricuspid regurgitation. Oesophageal varices may also be present. The mortality rate is determined by the severity of the underlying cardiac disease and not the liver disease.

Investigations

The diagnosis is not always obvious and right-sided heart failure must be considered in all patients with hepatomegaly with or without jaundice. The diagnosis is suggested by the triad of:

- Right heart failure;
- Hepatomegaly;
- Ascites (with high protein content in the presence of a high serum to ascites albumin gradient, along with refractoriness of ascites to diuretic treatment, which contrasts with resolution of peripheral oedema with diuretics).

Initial investigation includes:

- Liver biochemistry:
  - Hyperbilirubinaemia is mostly unconjugated and is seen in up to 70% of cases;
  - Bilirubin level increases with prolonged and repeated bouts of congestive heart failure and correlates with the right atrial pressure (but not cardiac output);
  - Alkaline phosphatase is only mildly elevated and aminotransferase elevations are mild unless cardiac output is impaired;
  - Hepatic synthetic function is usually preserved with a normal plasma albumin and prothrombin time;
  - Improvement in liver biochemistry with treatment of cardiac disease supports the diagnosis.
- Viral hepatitis serology.
- Abdominal ultrasound with Doppler studies of the liver (the discovery of dilatation of all three main hepatic veins on ultrasound mandates vigorous investigation for a cardiac cause).
- Liver biopsy may be useful in equivocal cases.
- ECG and echocardiogram.

Management

Management centres on treatment of the underlying heart disease. Jaundice and ascites usually respond well to diuresis. Repeated paracentesis may be necessary in the presence of refractory ascites. There is no need to regularly replace the albumin lost during paracentesis because synthetic function is preserved in congestive hepatopathy. It should be noted that liver disease rarely contributes to the morbidity or mortality in these patients, and serious complications, such as variceal bleeding and HCC, rarely develop.

Ischaemic/hypoxic hepatitis

Liver cell injury resulting from subcritical supply of oxygen to hepatocytes is traditionally classified as:

- Inadequate blood supply due to reduced hepatic arterial flow and/or passive venous congestion (e.g. heart failure) termed ischaemic hepatitis; or
- Hypoxic insult (e.g. respiratory failure), termed hypoxic hepatitis.

While the pathogenesis is multifactorial, the final common pathway is hepatocellular dysfunction secondary to critically low levels of oxygen for metabolic processes, and they will be considered together in this section under the term hypoxic hepatitis (HH).

Epidemiology and pathophysiology

Hypoxic injury to the liver is a reversible subclinical condition affecting at least 1% of critically ill patients and accounting for >50% of dramatic serum aminotransferase activity (24–48 h following the hypoxic insult) identified in hospital admissions.

The main aetiologies for HH include:

- Primary heart disease (78%);
- Congestive heart failure (65%);

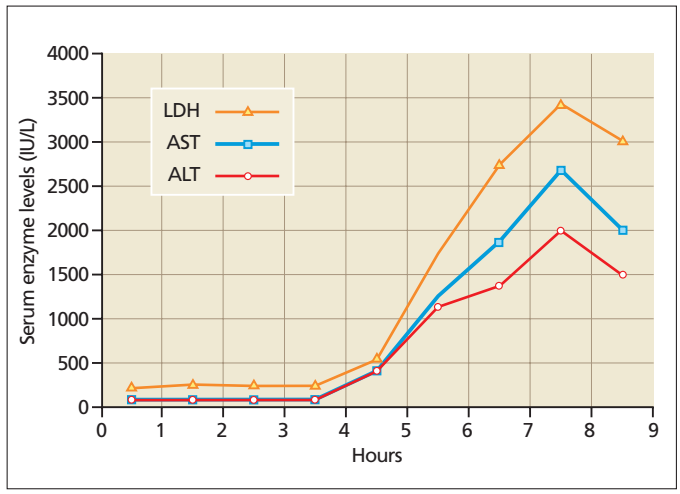

Figure 24.2 Degree of hepatic enzyme elevation over time post hypotensive injury.

- Acute myocardial infarction (17%);
- Chronic respiratory failure (12%);
- Circulatory shock and sepsis (15%) (sepsis alone, in the absence of shock, does not cause hepatic enzyme elevation)

The aetiology of the marked liver enzyme rise seen in HH is presumed to be hypoxic injury to the hepatocyte mitochondria and endoplasmic reticulum, especially to the centrilobular region. While hypotension/shock is a common antecedent to the onset of liver injury, severe hypotension/shock *per se* is unnecessary for the development of HH, which occurs frequently without hypotension due to forward (i.e. ischaemia) and backward (i.e. passive congestion) flow abnormalities, producing hypoxic injury through the common pathway of *hypoperfusion*, especially in the setting of systemic factors resulting in increased oxygen consumption or decreased oxygen availability.

The histological findings include central hepatic vein congestion with centrilobular hepatic necrosis, fragmentation of liver bulks, polymorphonuclear cell infiltration, abnormal hepatocyte complexes, pyknosis and disintegration of hepatocyte nuclei. Hyperplasia, inflammation and regeneration, which are characteristic of many other forms of hepatitis, are absent.

Clinical features

Frequently the liver injury is subclinical, with only non-specific nausea and vomiting. The liver may be tender and enlarged.

Risk factors for HH may be present (acute and chronic heart failure, respiratory failure, sepsis, prolonged hypotension, toxin ingestion and heat stroke).

Investigations

The diagnosis is based on clinical and biochemical criteria generally without the need for procedural intervention. There is a profound transient serum enzyme elevation in conjunction with abnormal renal function and abnormalities in PT and APTT activity (Figure 24.2). There are no biochemical differences that distinguish between patients with injury caused predominately by hypotension *versus* non-hypotensive, non-hypovolaemic patients with hypoxic hepatopathy.

Management

Management is purely supportive and focuses on correcting the underlying conditions leading to hypotension, and hypoxic and hepatic hypoperfusion, including congestion.

Prognosis

The prognosis depends on that of the underlying disease, being largely independent of the liver injury. That said, the occurrence of hypoxic hepatopathy is a harbinger of a potentially poor prognosis since the mortality rate varies from 25% to 73%.

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Autoimmune hepatitis

A rare autoimmune condition, autoimmune hepatitis (AIH) is diagnosed by the presence of a constellation of clinical, laboratory and pathological features. The disease usually responds to corticosteroid treatment, although relapses on stopping therapy are common. The immune biliary conditions primary biliary cirrhosis (PBC) and sclerosing cholangitis (PSC) are considered in Chapter 19.

Epidemiology and pathophysiology

AIH is a condition of unknown cause, which particularly affects young females of any age. However, both sexes and all ethnicities may be affected. It is associated with concurrent immune disease. It is relatively common for AIH to recur or develop *de novo* after liver transplantation and the diagnosis must be considered in all transplanted patients with allograft dysfunction.

While the exact pathogenesis is unknown there are identified aetiological triggers, in particular drugs (Table 25.1). The principal effector cells of the autoimmune process in AIH are the CD4+ and CD8+ T lymphocytes. The regulatory CD4+ CD25+ T cells are decreased in number and function and so fail to modulate CD8+ T-cell proliferation and cytokine production, thus facilitating liver injury. This activity can be modulated by genetic factors, in particular the HLA haplotype. The association between AIH and the class II antigens of the major histocompatibility complex (MHC) varies between ethnic and geographical groups. Corticosteroids reconstitute the T-regulatory cell function and attenuate the cell-mediated cytotoxic response in AIH.

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Clinical features

- Clinical presentation is often acute, and rarely fulminant, and may mimic acute viral or toxic hepatitis.
- There are also indolent, asymptomatic forms of the disease:
  - Commonest complaints are of fatigue, amenorrhea and those associated with an accompanying rheumatological disorder such as arthritis or thyroid disease;
  - Physical findings include jaundice (in severe disease), spider naevi, palmar erythema and hepatosplenomegaly.

Concurrent immune diseases may obscure the underlying liver disease. The associated immune conditions include systemic sclerosis, polymyositis, neuritis multiplex and polyglandular autoimmune syndrome type III.

Investigations

- **Blood testing**:
  - Autoantibodies are the hallmark of AIH: particularly antinuclear factor and smooth-muscle antibodies. The disease is often subclassified into type 1 and type 2, the latter demonstrating antibodies to liver/kidney microsome (anti-LKM 1 hepatitis);

Table 25.1 Drugs implicated in the aetiogenesis of autoimmune hepatitis.

First implicated drug	DialosePlus® (dioctylsodium sulphosuccinate, carboxymethyl cellulose, oxyphenisatinacetate) First report of AIH in1971; over 100 cases since then, removed from market	
Type 1 AIH-like liver disease	Multiple reports: • Oxyphenisatin • Nitrofurantoin • Minocycline • Alpha-methyldopa • Clometacine Few reports – herbal compounds: • Dai-saiko-to • 3,4-methylenedioxy-metamphetamine ('Ecstasy') • Morindacitrifolia (Nonijuice)	Few reports – conventional drugs: • Papaverine • Diclofenac • Doxycycline • Phenprocoumon • Fenofibrate • HMG-CoA reductase inhibitors (artorvastatin, rosuvastatin, simvastatin) • Rifampin + infliximab • Pyrazinamide • Interferon
Type 2 AIH-like liver disease	Dihydralazine Tienilic acid Halothane Black cohosh (*Actaea racemosa)*	

  - Hypergammaglobulinaemia, with pronounced elevation of IgG levels is invariable. Serum Ig levels can be useful in monitoring response to treatment and are predictive of future flares;
  - Reduced serum albumin is common.
- **Liver biopsy**: essential both for diagnosis and assessment of severity, as well as to exclude other liver disease. Characteristically this shows an interface hepatitis which may coexist with cirrhosis.

The important differential diagnosis is with PBC, which differs from AIH by:

- Immunohistochemistry demonstration of nuclear envelope protein, gp210;
- Less marked serum aminotransferase elevations, absence of antinuclear antibodies;
- Histological changes of greater bile duct injury than interface hepatitis.

Management

If untreated AIH may progress rapidly to cirrhosis within 3–5 years.

- Mainstay of treatment is high-dose corticosteroids (prednisone 40–60 mg/day) for 4–6 weeks, then tapered to a maintenance level (e.g. 5–10 mg/day):
  - Aim is to keep the liver enzymes within normal values;
  - This may not prevent fibrosis, but is lifesaving in this otherwise fatal condition;
  - On stopping corticosteroids many patients relapse and treatment failure and drug toxicities are all too common.
- Often azathioprine is added for its steroid-sparing effect. With this strategy the frequency of relapse can be reduced from 93% to 60%.
- Other immunosuppresives, including tacrolimus, mycophenolate mofetil and rapamycin, have been used empirically as frontline and salvage treatments for problematic patients.
- In those not responsive to, or who relapse on, conventional therapy, liver transplantation is highly successful.

Prognosis

Prognosis is determined by the diseases response to corticosteroid. Responsiveness is similar in all age groups. Disease onset during pregnancy carries a relatively high risk of an adverse outcome and high rates of postpartum exacerbation.

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Non-alcoholic fatty liver disease

Epidemiology and pathophysiology

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term (Figure 26.1) encompassing simple steatosis (fatty liver) without liver inflammation, non-alchoholic steatohepatitis (NASH), where as a result of fatty infiltration there is inflammation of the liver and the risk of liver damage, and fibrosis and cirrhosis resulting from NASH.

NAFLD affects all age groups, including children, with an equal sex distribution. Its prevalence increases with increasing body weight, affecting 10–15% of normal individuals and up to 80% of the obese. NASH follows a similar pattern, affecting 3% of normal individuals and 20% of the morbidly obese (BMI > 35 kg/m^2).

Most NAFLD is primary (idiopathic), but it can occur in association with rare disorders of lipid metabolism and insulin resistance, including:

- Abetalipoproteinaemia.
- Lipoatrophic diabetes.
- Mauriac and Weber–Christian syndrome.
- Iatrogenic:
  - Parenteral nutrition;
  - Acute starvation;
  - IV glucose therapy;
  - Abdominal surgery;
  - Drugs (amiodarone, tamoxifen, synthetic oestrogens and glucocorticoids).

NAFLD is principally associated with the metabolic syndrome and a 'two hit' model of pathogenesis has been proposed:

- First 'hit' consists of excessive triglyceride accumulation in the liver:
  - Driving factor is insulin resistance;
  - This primarily involves the muscles and adipose tissue and results in hyperinsulinaemia;
  - Liver remains insulin sensitive, resulting in increased hepatic uptake of free fatty acids (FFAs) and increased hepatic triglyceride synthesis;
  - This results in net hepatic fat accumulation. FFAs impair insulin signalling and cause further insulin resistance.
- Steatotic liver is then vulnerable to 'second hits', resulting in inflammation and liver damage:
  - Increased FFA oxidation produces hepatotoxic free oxygen radicals which contribute to oxidative stress and contributes to the 'second hit';
  - Other contributors to the second hit include:
    - Pre-existing mitochondrial abnormalities;
    - Cytokine production (e.g. tumour necrosis factor-α);
    - Defects in peroxisome proliferator activating receptors (PPARs, which are involved in triggering the effects of insulin);
    - Resistance to leptin.

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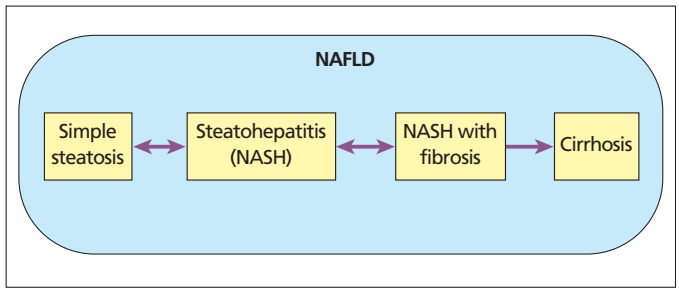

Figure 26.1 Spectrum of non-alcoholic fatty liver disease (NAFLD).

Prognosis and natural history

Patients with NAFLD have a slightly higher mortality than the general population. The natural history has not been clearly defined and estimates of the risk of NASH progressing to cirrhosis range between 8% and 15%. NASH progresses to cirrhosis less frequently than alcoholic steatohepatitis and has a better long-term survival. Even once NASH results in fibrosis, deterioration is not inevitable: fibrosis progresses in about a third, remains stable in a third and regresses in a third. The clinical and biochemical factors associated with risk of progression include:

- Increasing age;
- Obesity;
- Pronounced weight loss (especially if previously obese);
- Diabetes mellitus;
- AST/ALT ratio > 1;
- ALT more than two times normal and raised triglycerides.

Clinical features

The symptoms of NAFLD, when there are any, are generally mild and non-specific (most commonly right upper quadrant abdominal pain). Most patients have no symptoms at all and the diagnosis is most commonly made incidentally. A detailed history of alcohol consumption should be obtained. The findings on examination are those of the metabolic syndrome: commonly obesity (especially abdominal obesity), the complications of diabetes, hypertension and acanthosis nigricans (a dark pigmentation of the skin of the armpits and neck associated with insulin resistance). The liver usually feels normal, however hepatomegaly may occur.

Investigations

Most commonly NAFLD is an accidental finding. There is no biochemical or imaging modality currently that can differentiate simple fatty liver from NASH.

The hallmark of NAFLD is macrovesicular steatosis in the absence of alcohol excess (<40 g of ethanol/week). In practice the diagnosis is made where there are persistently elevated LFTs, a negative alcohol history and other causes of fatty liver have been excluded. If weight loss results in a decrease or normalisation of the liver enzymes, the diagnosis of NAFLD is practically assured. Given the association with the metabolic syndrome, all patients should have fasting sugars and lipids measured.

The *transaminases* are mild to moderately elevated but can fluctuate from month to month. Typically the ALT is greater than the AST, in contrast to alcoholic liver disease where the reverse is true.

Initial *imaging* is usually with ultrasound which frequently shows a hyperechoic liver; however, this finding is neither sensitive nor specific.

Liver biopsy allows diagnosis, differentiation of simple steatosis from NASH and some assessment of disease severity and possibly prognosis. However, there remains no international consensus regarding when liver biopsy should be performed or the histopathological criteria that would firmly define NASH and differentiate between NAFLD entities. A scoring system, the 'NAFLD Fibrosis Score' has been developed as a way of predicting fibrosis (hence potentially avoiding need for biopsy in this common condition) and stratifying into outcome categories (Box 26.1).

Box 26.1 Components of the NAFLD Fibrosis Score.

- Age
- Hyperglycaemia
- Body mass index
- Platelet count
- Albumin
- AST/ALT ratio

Management

- Lifestyle modification is the main therapy. Short-term weight loss in combination with exercise leads to improvement in liver biochemical tests and to resolution of hepatic steatosis. The aim is for moderate weight loss as overly rapid weight reduction could aggravate steatohepatitis. Multiple weight reduction therapies have been investigated but bariatric surgery is perhaps the best therapeutic modality in the presence of severe obesity.
- Elevated cholesterol, triglycerides and blood sugar should be corrected.
- In diabetic patients, HbA_{1C} should be reduced to < 7%.
- Pharmacological therapy is only considered when there is no change in the condition after lifestyle modification.

27

Alcoholic liver disease

Epidemiology and pathophysiology

Alcohol misuse is a major public health problem, the World Health Organization estimating that 140 million people globally suffer from alcohol dependence. Alcoholic liver disease (ALD) encompasses a spectrum of diseases ranging from fatty liver to alcoholic hepatitis to cirrhosis. The main risk factor is the quantity and duration of alcohol ingestion. In addition, nutritional status and genetic and metabolic traits play a role. The main genetic factors are polymorphisms in the genes responsible for ethanol metabolism, aldehyde and alcohol dehydrogenases (ALDHs and ADHs, respectively) and cytochromes P450 (CYPs). The male-to-female ratio is 11:4. Differences in body water composition mean that women are more susceptible than men to the harmful effects of alcohol.

The main pathogenic mechanism for liver damage is oxidative stress, arising from:

- Changes in the redox state of the hepatocytes;
- Elevation of hepatocyte Kupffer iron;
- Reactive acetaldehyde derivatives;
- Mitochondrial damage;
- Reduced cellular antioxidants;
- Alterations in intracellular signalling;
- Action of inflammatory cytokines, adipokines and hormones (Figure 27.1).

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The pathology of ALD is considered a continuum from fatty liver through alcoholic hepatitis on to cirrhosis, although in practice these features often overlap:

- **Fatty liver** is the initial, reversible, effect:
  - Consists of the accumulation of cytoplasmic macrovesicular triglceride droplets which displace the nucleus;
  - Less often there are microvesicular accumulations, which do not displace the nucleus, representing mitochondrial damage.
- **Alcoholic hepatitis** is the next step:
  - Results from the combination of fatty liver and inflammation with necrosis of hepatocytes;
  - Hepatocytes develop a swollen and granular cytoplasm (termed 'balloon degeneration');
  - Deposition of fibrillar protein and clumping of organelles in the cytoplasm (termed 'Mallory', or alcoholic, hyaline bodies).
- **Cirrhosis** occurs when advanced liver disease disrupts the normal liver architecture:
  - Collagen fibrosis of the terminal venules compromises perfusion and contributes to portal hypertension;
  - Regeneration is typically limited to the production of small nodules (micronodular cirrhosis), although, particularly with abstinence, macronodular cirrhosis can occur;
  - Iron accumulation in the hepatocytes occurs in up to 10% of patients.

Zieve's syndrome refers to a clinical state distinct from the above progression of disease (Box 27.1).

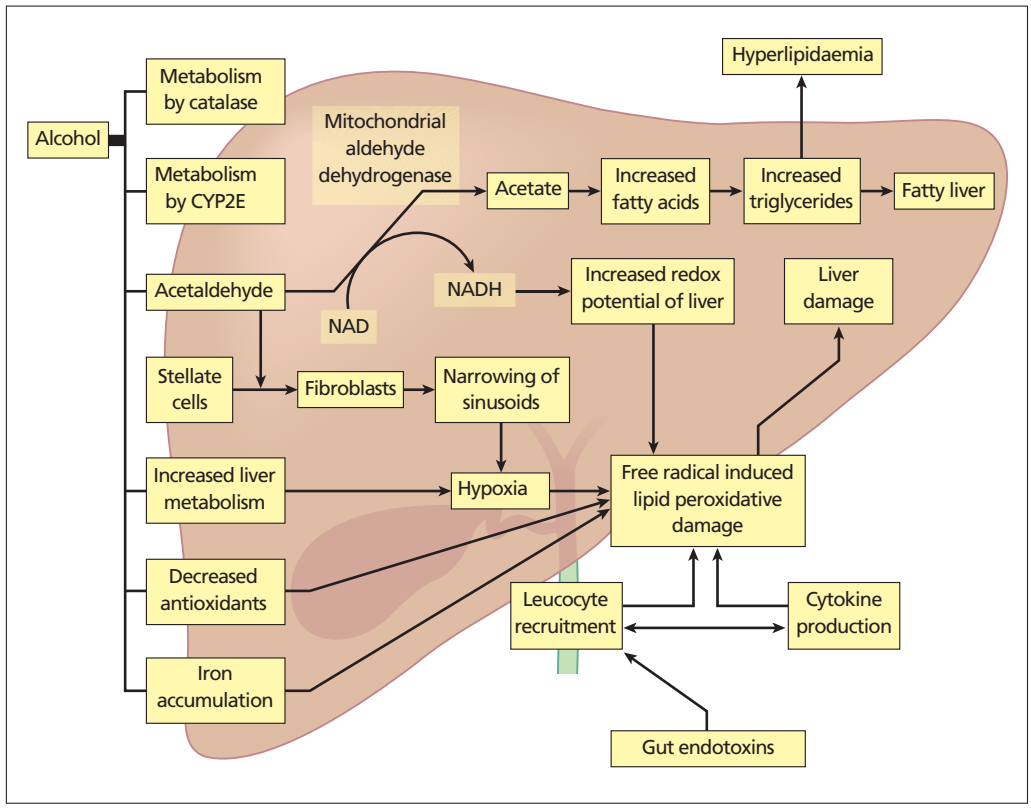

Figure 27.1 Pathophysiological consequences of alcohol on the liver.

Box 27.1 Features of Zieve's syndrome.

Alcohol excess with:

- Alcoholic hepatitis
- Haemolysis
- Jaundice
- Abdominal pain
- Hyperlipidaemia

Box 27.2 Features of alcoholic hepatitis.

- Tiredness, non-specific ill health
- Hepatomegaly, ascites
- Mild liver enzyme abnormalities
- Severity: encephalopathy *or* jaundice and elevated INR
- Histology: Mallory's hyaline, balloon degeneration, neutrophil infiltration
- Treatment: prednisolone for moderate–severe disease
- Alternative treatment: pentoxifylline, a phosphodiesterase inhibitor which is thought to work through an anti-TNF mechanism

Clinical features

Fatty liver

- Generally asymptomatic;
- Occasionally may cause anorexia, nausea and right upper quadrant pain (usually follows a prolonged, heavy alcoholic binge).

Alcoholic hepatitis (Box 27.2)

- Wide range from mild (limited, non-specific symptoms) to severe (fulminant).
- Moderate:

- 2–3-week prodrome of fatigue, anorexia, nausea and weight loss;
- Malnutrition is prominent;
- Mild fever (<40°C), jaundice and tender hepatomegaly.

- Severe:
  - Usually follows a period of drinking and eating very poorly;
  - Gravely ill with fever, marked jaundice, ascites and evidence of a hyperdynamic circulation (marked palmar erythema is common), spider naevi, parotid enlargement and gynaecomastia;
  - Hypoglycaemia is common and can result in coma;
  - GI bleeding, usually due to a local gastric duodenal lesion, is common.

Cirrhosis

- Symptoms are those for any cause of cirrhosis (see Chapter 20).
- May be additional alcohol-related toxicities:
  - Peripheral neuropathy;
  - Wernicke's encephalopathy (ataxia, ophthalmoplegia, confusion, impaired short-term memory);
  - Korsakoff's psychosis (amnesia, confabulation, apathy);
  - Hypogonadism and feminization (in men).

Investigations

Diagnosis requires suspicion of alcohol as a cause of liver disease, remembering that patients may not always give an accurate alcohol history. CAGE and the alcohol use disorders identification test (AUDIT) are useful screening tools for the presence of an alcohol problem (Box 27.3).

No specific test exists for ALD.

All *blood tests* suffer from the limitations of specificity:

- Serum gamma-glutamyl transferase (GGT) increases due to enzyme induction.
- Red-cell mean corpuscular volume (MCV). Macrocytosis is a result of the effects of folate deficiency and alcohol on the bone marrow.
- Serum carbohydrate-deficient transferrin (CDT): relatively more specific for ALD than the other tests.

Box 27.3 CAGE questionnaire to identify alcohol misuse.

This screening test is short and simple to administer. Two or more positive answers are correlated with alcohol dependence in 90% of cases. CAGE may not pick up problems in those who are fearful of negative consequences of disclosure (e.g. those looking for accommodation, or who are fearful of child protection issues) and those with mental health problems.

C – Have you ever thought you should CUT DOWN on your drinking?
A – Have you ever felt ANNOYED by others' criticism of your drinking?
G – Have you ever felt GUILTY about your drinking?
E – Do you have a morning EYE OPENER?

- Elevations of the aminotransferases are generally moderate (<300 IU/l) and do not reflect the degree of liver damage:
  - AST exceeds ALT (AST/ALT > 2);
  - Relatively low ALT is due to dietary deficiency of pyridoxal phosphate (vitamin B_6).
- Bilirubin and INR: severity of disease is related to the bilirubin (indicator of secretory function) and INR (synthetic function).
- All patients should have screening tests for treatable causes of liver disease, especially viral disease.

Liver biopsy is useful to confirm the diagnosis, stage the severity of the disease and rule out other liver conditions.

Management

- Abstinence is the mainstay of treatment.
- General supportive care:
  - Nutritious diet;
  - Vitamin (particularly B vitamin) supplementation, especially in the first few days of abstinence;
  - Withdrawal from alcohol is treated with benzodiazepines.

- Corticosteroid use is controversial but may be beneficial for patients with severe alcoholic hepatitis complicated by encephalopathy.
- Trials of other drugs (propylthiouracil, colchicines) have not shown sustained benefit.
- Liver transplantation gives 5-year survival rates comparable to those after transplantation for non-alcoholic liver disease. However, about 50% of patients resume drinking after transplantation, so most programmes require 6 months of abstinence and assurance that good social networks are in place.

Prognosis

Once cirrhosis develops patients who abstain have a 5-year survival rate of 60–70%, which falls to 40% in those who continue to drink. Negative prognostic indicators include:

- Low serum albumin;
- Increased INR/PT;
- Low haemoglobin;
- Encephalopathy;
- Persistent jaundice;
- Azotemia.

Hepatocellular carcinoma occurs in 10% of stable cirrhotics, usually developing after a period of abstinence when macronodular cirrhosis is present.

28

Liver tumours and lesions

Classification of liver lesions revolves around whether the lesion is likely to be benign or malignant. The degree of certainty of this will determine the need for further imaging or biopsy. Table 28.1 details each of the main liver lesions.

Clinical features

The vast majority of liver lesions are asymptomatic and are discovered incidentally when imaging is performed for another reason. In this situation, the history and examination are directed at discovering risk factors for, and features of, underlying hepatic disease or systemic conditions associated with liver lesions. The two clear exceptions are when:

- Patient is undergoing surveillance for hepatocellular carcinoma (HCC);
- Liver mass was discovered because it is palpable.

These situations obviously incur a different range of likely diagnoses and are frequently associated with more sinister pathologies.

Investigations

Serology

- FBC and biochemistry, primarily aimed at detecting underlying liver dysfunction or associated pathology.
- Raised levels of alpha-fetoprotein (AFP) are indicative of HCC in the right clinical setting. Other tumour markers, while not specific or sensitive, may guide diagnostic decision-making.

Radiology

- Ultrasound remains the initial study of choice:
  - Advantages include safety, minimal necessary pre-examination preparation and relatively low cost.
  - Preferred modality for serially imaging of lesions to monitor for progression.
- Next modality of investigation, if needed, depends on the differential diagnosis based on the ultrasound features: CT and MRI most commonly.

Biopsy

After the discovery of a liver lesion, liver biopsy might be required to either determine:

- Diagnosis, including the presence or absence of malignancy. or
- Presence or absence of underlying liver disease and cirrhosis.

Biopsy is avoided if HCC or hydatid is strongly suspected, to avoid the risk of 'seeding' the tumour along the biopsy tract.

Management

The vast majority of benign liver lesions require no active treatment. The main exceptions are when a large lesion close to the capsule of the liver is causing pain or when central lesions cause biliary

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Table 28.1 Cardinal features of the commonest liver tumours.

		Clinical features	Radiological features	Diagnosis	Treatment	Prognosis
Benign liver tumours	**Hepatocellular adenoma**	Women of childbearing age Associated with oral contraceptives Mostly asymptomatic Large lesions may cause RUQ discomfort Rarely, peritonitis and shock due to rupture and intraperitoneal haemorrhage	Usually involving the right lobe Often hypervascular but with hypovascular areas	Biopsy usually needed for confirmation and to rule out malignant transformation	Adenomas due to contraceptive use often regress if the drug is stopped Resection of larger, symptomatic tumours only	Very rarely undergo malignant transformation
	Focal nodular hyperplasia	Female predominance May resemble macronodular cirrhosis Multiple tumours in 20% Not related to the oral contraceptive	Stellate fibrous septae ('stellate scar') Presence of Kupffer cells shows as an area of increased uptake on radionuclear scanning MRI: lesions usually hypointense to liver on T_1 and T_2 (scar may be hyperintense on T_2)	Diagnosis usually based on contrast MRI or CT Biopsy may be necessary Solid tumours have a fibrous core and include other cell types (atypical hepatocytes, Kupffer cells and inflammatory cells)	Treatment is rarely needed (especially if asymptomatic)	Haemorrhage in only 2–3% (most common complication)
	Haemangioma	Found in 0.5–7% of the general population Usually asymptomatic More common in women	Ultrasound: increased echogenicity CT: decreased density, enhances from periphery	Radiological	Does not require any treatment	Rupture is rare, even in large tumours No malignant potential

Hepatic cysts	**Benign hepatic cysts**	Idiopathic, rarely associated with polycystic kidneys, usually asymptomatic and have no clinical significance	Isolated cysts are commonly detected incidentally on abdominal ultrasound or CT	Radiological	Not necessary	Rare congenital condition, polycystic liver commonly associated with polycystic disease of the kidneys True cystic tumours rare
	Hydatid cysts	Tapeworm of the genus Echinococcus Endemic areas: Mediterranean, Middle East, South America, Iceland, Australia, New Zealand, Southern Africa	Ultrasound may demonstrate classical daughter cysts and 'hydatid sand' CT highly sensitive and specific	Parasite serology and radiological features Biopsy avoided	Surgical treatment of larger and superficial cysts Medical treatment: albendazole or mebendazole 3–6 months Emerging use of puncture, aspiration, injection, and re-aspiration technique	Morbidity is usually secondary to free rupture of the echinococcal cyst (with or without anaphylaxis), infection of cyst, Biliary obstruction, cirrhosis
	Caroli's disease	Rare autosomal recessive disease Usually detected in childhood or early adulthood Associated with medullary sponge kidney (renal tubular ectasia) in 80%	Characterised by segmental cystic dilation of intrahepatic bile ducts	MRCP or ERCP	Treatment for complications	No associated cirrhosis or portal hypertension Predisposed to calculus formation Prone to recurrent cholangitis and resultant liver abscesses Increased risk of cholangiocarcinoma

(*continued*)

Table 28.1 Cardinal features of the commonest liver tumours (*continued*)

		Clinical features	Radiological features	Diagnosis	Treatment	Prognosis
Malignant liver tumours	**Primary liver cancer (HCC)**	Male predominance Usually cirrhotic Risk greatest in: • Chronic hepatitis B (cirrhotic and non-cirrhotic) • Hepatitis C • Haemochromatosis • Cirrhosis from α-1-antitrypsin deficiency Worldwide incidence 1 million cases per year Risk of HCC in cirrhosis 1–6% per year	CT: isodense lesion surrounded by a low-density contrast-enhancing ring Associated with portal vein thrombosis	Serum α - fetoprotein levels (AFP) are > 500 μg/l in 70–80% of cases Biopsy often not needed when characteristic radiology and cirrhosis	Treatment is disappointing Resection often complicated by the presence of underlying cirrhosis, multiple lesions and micrometastases Liver transplantation may be considered for multiple lesions and cirrhosis	Up to 70% of patients already have metastatic disease at the time of diagnosis Mean survival from time of diagnosis is 6–12 months
	Metastatic liver cancer	Accounts for 95% of all hepatic malignancies 50% of malignancies in cirrhotic liver Majority associated with end- stage disease Colonic adenocarcinoma commonest cause of potentially curable solitary metastases	CT: lesions generally hypovascular and hypoattenuating when imaged during portal venous phase Intraoperative ultrasound useful for detecting liver metastases at surgery	Characteristic radiology and known primary usually sufficient Biopsy may help to determine diagnosis and treatment if primary lesion not found	Approximately 20% colorectal liver metastases are resectable Neoadjuvant systemic chemotherapy may increase number resectable	'Curative' resection 5-year survival rate of 25–38% Non-operative therapy only provides a median survival rate of 9 months

Fibrolamellar carcinoma	Distinct variant of HCC Young adults No association with pre-existing cirrhosis, viral hepatitis or other known risk factors	Lobulated heterogeneous mass with a central scar in an otherwise normal liver	Characteristic morphology of malignant hepatocytes enmeshed in lamellar fibrous tissue AFP levels are rarely elevated	Initial treatment usually involves resection of the primary tumour or liver transplantation, with *en bloc* resection of metastatic lymphadenopathy	Prognosis is better than for HCC Many patients survive several years after tumour resection Tumour recurrence common and almost always involves the liver
Cholangiocarcinoma	Second most common primary liver tumour Male predominance Predisposing: primary sclerosing cholangitis, choledochal cysts	Features helpful in differentiating from other primary tumours: • Homogeneously echogenic or high attenuation • Presence of calcification • Invasion of portal or hepatic veins uncommon	Histology necessary May require exploratory laparotomy for adequate biopsy Endoscopic ultrasound may be useful for imaging and biopsy	Approximately 30% are resectable at time of diagnosis	Overall survival rate after resection dependent upon tumour staging, tumour-free surgical margins and lymph node status
Hepatoblastoma	Affects children, almost all < 3 years old	Right lobe (75%), both lobes or multicentric (33%)	Increased AFP in 67–90%	Surgical resection only curative option Control of metastatic disease with adjuvant chemotherapy 30% resectable at presentation	Metastases at diagnosis in 10%

obstruction. Treatment of malignant lesions depends on the condition and the underlying liver disease.

Metastatic liver cancer

Many malignant conditions metastasise to the liver as a late feature of terminal disease. Only colorectal adenocarcinoma (commonest) and neuroendocrine tumours present as solitary metastases to the liver and are potentially curable. Approximately 20% of patients with colorectal liver metastases have disease that is resectable at the time of diagnosis. Curative resection gives 5-year survival rates of 25–38%; non-operative therapy only provides a median survival rate of 9 months. Neoadjuvant systemic chemotherapy may increase the proportion of patients with resectable disease.

Hepatocellular carcinoma

Treatment of HCC localised to the liver depends on the presence or absence of cirrhosis. Survival is usually not > 6 months in patients with a large tumour mass and Child C cirrhosis. Patients with small HCCs (<5 cm diameter) and stable liver function have a better prognosis but survival rates are still only 21% at 3 years. Surgical resection is recommended for patients without cirrhosis or with limited segmental or lobar HCC and preserved hepatic function. Transplantation is mainly recommended when the tumour is small, extrahepatic disease is non-existent and hepatic reserve is poor.

29

Pregnancy-related liver disease

Liver disease in pregnancy may take the form of problems that occur more frequently in pregnancy (e.g. gallstones) or run a more serious course (e.g. acute hepatitis E); coincident liver disease which may affect management or have implications after delivery (e.g. chronic hepatitis B and C); or liver diseases specific to pregnancy. The latter are the most common cause of liver dysfunction in pregnancy and it is these that are considered in this chapter.

In recognising pregnancy-related liver disease the clinician must be aware of the normal physiological changes affecting the liver in pregnancy. Generally speaking, palmar erythema, spider angiomas, low serum albumin levels and high serum alkaline phosphatase levels are benign changes in the liver during pregnancy. High levels of serum liver aminotransferase or bilirubin signal a problem.

HELLP syndrome

The HELLP syndrome may be thought of as a severe form of pre-eclampsia. Pre-eclampsia itself is a condition, occurring after 20 weeks' gestation, consisting of a triad of hypertension, proteinuria and oedema. The lungs and brain are the most vulnerable organs in pre-eclampsia. It often causes abnormal LFTs (modest elevation of serum transaminases and occasionally mild hyperbilirubinaemia), but does not usually seriously affect the liver.

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Clinical features

The HELLP syndrome, in contrast, is associated with significant hepatic dysfunction. A syndrome of Haemolysis, Elevated Liver enzymes and Low Platelets on a background of pre-eclampsia or eclampsia defines it. The HELLP syndrome complicates 0.1% of pregnancies, and is associated with poor maternal and neonatal outcomes. Patients may present from 20 weeks' gestation but the syndrome usually occurs between 27 and 36 weeks. Presentation is non-specific – abdominal pain, nausea and sometimes headache.

Investigations

- Nadir platelet count and peak transaminase levels are a reflection of disease severity.
- While the haemoglobin level may be normal initially, haemolysis occurs, with the deformed red cells of microangiopathy visible on blood film, and often a marked decrease in the haemoglobin.
- Renal dysfunction is common.
- Clotting must be monitored but remains normal except in advanced disease with the onset of disseminated intravascular coagulation.

Management

- Treatment is by delivery as soon as is practicable, balancing maternal health and fetal outcome. In uncomplicated disease, once 34 weeks' gestation is reached, this decision is not difficult. However, in complicated disease or early gestation the balance is not straightforward.
- Where organ failure occurs, immediate delivery is dangerous and must be preceded by transfer to intensive care and rapid correction of fluid

imbalance, hypertension, hypoxia, seizures and coagulopathy:
  - Dexamethasone promotes maturity of the fetal lungs and ameliorates HELLP;
  - Most serious complications stem not from liver disease but the other effects of this severe form of pre-eclampsia, although rarely subcapsular haematoma and resultant liver rupture is fatal;
  - While with aggressive management and improved disease recognition maternal mortality has fallen below 1%, perinatal mortality is still 10–20%.
- Medical treatment in an attempt to ameliorate disease and gain gestational time (plasma volume expansion, vasodilatation, low-dose Aspirin, corticosteroids) are advocated, but have not been subjected to controlled trials.

Acute fatty liver of pregnancy

Epidemiology and pathophysiology

Acute fatty liver of pregnancy (AFLP) results in hepatic failure, and maternal and fetal mortality. Originally considered rare, it is now recognised that AFLP occurs relatively commonly in a less severe form which is associated with better outcomes. Incidence is estimated at 1 in 1000 deliveries. There are no clear geographical or racial predispositions to AFLP. Risk factors for disease include older maternal age, primiparity, multiple pregnancies, pre-eclampsia, male fetus and previous AFLP.

The pathophysiology is one of microvesicular fatdeposition. In a minority of cases this can be attributed directly to an inherited defect of fatty acid oxidation, but the majority of affected mothers do not have such a deficiency and the cause of AFLP remains unknown.

The characteristic histological features are swollen foamy hepatocytes due to microvesicular fat. The architecture is not disturbed and neither inflammation nor necrosis is prominent, but some cholestasis is common.

Clinical features

- AFLP occurs at 32–36 weeks' gestation, presenting non-specifically (nausea, abdominal pain).
- Polyuria and polydipsia are common, sometimes diabetes insipidus.
- Jaundice and encephalopathy only occur late.
- Pancreatitis is frequently associated, but because the symptoms are similar to AFLP the diagnosis is difficult.
- There are no specific examination features and examination is often normal.

Investigations

The features are of acute impairment of hepatic function in late pregnancy. Biopsy is often contraindicated in the face of severe disease but when performed shows characteristic histological features (see above).

Typical laboratory findings are:

- Neutrophilia (present in almost all cases), platelet count which initially is normal but drops with disease progression and normal haemoglobin.
- Transaminases are moderately elevated and renal dysfunction is common.
- Antithrombin III activity is profoundly and consistently decreased.
- Hyperammonaemia, coagulopathy and hypoglycaemia are early features that assist in differentiating AFLP from HELLP (the main differential diagnosis: the presence of polyuria and polydipsia, and early absence of anaemia are also useful in this regard).
- Radiological imaging is not particularly helpful as microvesicular steatosis is not easily detected.

Management

Early delivery is the mainstay of treatment. The safest way of achieving this is emergency caesarean section in combination with ICU management of coagulopathy, renal dysfunction, acidosis and sepsis. Occasionally, liver transplantation is required. Maternal death is uncommon and the rate of perinatal death is <10%. It should be noted that AFLP may recur in subsequent pregnancies.

Obstetric cholestasis

Epidemiology and pathophysiology

There has been an apparent increase in the incidence of obstetric cholestasis (OC) or intrahepatic

cholestasis of pregnancy. This is at least in large part an artefact of better case ascertainment with the increasing investigation of the symptom of pruritis in pregnancy. The pathophysiology is of pure cholestasis without hepatic inflammation or necrosis.

No single cause is responsible for all cases. Important factors influencing the incidence of the disease include:

- Ethnicity (Asians being at greater risk).
- Environment (possible association with low selenium levels).
- Hormonal effects, as demonstrated by the increased incidence in late pregnancy and multiple pregnancies, and precipitation by exogenous progestogens.
- Genetic influences, with a strong familial tendency and the discovery of specific gene mutations in a minority of cases.

Clinical features

- Patients present with generalised pruritis, which particularly involves the palms and soles and is worst at night. This tends to occur at 30–36 weeks' gestation but can start as early as the first trimester.
- Jaundice is not common, occurring in <10%, and when it occurs it indicates more severe cholestasis.
- Family history is common (up to 30%).
- Urinary infection often precipitates, or is associated with, OC.

Investigations

- It must be noted that the laboratory findings of OC are not those normally expected with cholestasis. The observed elevation of serum transaminases (up to 10 times normal)may be explained by increased membrane permeability. It does not necessarily occur at the onset of pruritus and transaminase elevation in an otherwise well woman with pruritus in pregnancy is virtually diagnostic of OC.
- ALP is not useful as it is mildly elevated in late pregnancy normally. GGT is raised in only 30% of cases.
- Serum bile acids are more sensitive and specific. Bilirubin may be slightly elevated in about 10%.
- Imaging is not usually contributory.

Management

The main effect of this disease is not on the mother but on the fetus, with increased rates of prematurity, fetal distress and stillbirth. Fetal outcome may be influenced by peak bile acid levels.

Treatment traditionally consists of:

- Ursodeoxycholic acid (UDCA) is the treatment of choice. It reduces maternal bile acid levels and affects pruritis. As yet there is no evidence that it affects perinatal mortality; given the very low mortality rate of <1%, a very large number would be required for such a trial.
- Antihistamines and cholestyramine may have a slight effect.
- Delivery is recommended at 36–38 weeks as the risk of stillbirth increases beyond 36 weeks' gestation. Older studies reported perinatal mortality as high as 10%; however, with current active management this appears now to be <1%.

The features of OC resolve rapidly after delivery, usually within a few days. If abnormalities persist, the diagnosis should be reconsidered. There is a high (50–75%) rate of repeat OC in future pregnancies.

Hyperemesis gravidarum

Nausea and vomiting are common in early pregnancy. In contrast, hyperemesis, defined as severe intractable vomiting requiring admission, occurs in <1%. It is commoner in younger, obese, multiparous women and twin pregnancies.

The onset of disease is at 4–10 weeks' gestation. LFTs are deranged by up to 50%, with transaminase elevation between 2 and 10 times normal. Jaundice is uncommon. Invasive tests are not warranted.

Most cases settle with rehydration, electrolyte replacement and glucose. Symptoms typically resolve after 20 weeks' gestation. If improvement is slow, parenteral hydrocortisone sometimes leads to rapid resolution. Maternal and fetal outcomes are not influenced, providing dehydration is avoided.

30

Liver transplantation

Indications and contraindications

Orthotopic liver transplantation (OLT), when required, is indicated for most causes of acute or chronic liver disease. Cirrhosis accounts for > 80% of transplants performed in adults, hepatitis C and alcoholism being the two most common underlying diagnoses.

There are very few absolute contraindications to OLT:

- Anatomic abnormality precluding transplant;
- Malignancy outside the liver;
- Untreated sepsis;
- Advanced cardiopulmonary disease;
- Active alcohol and drug use.

However, conditions previously considered contraindications, such as HIV infection and older age, are now only relative considerations in many centres.

Preparation

Prior to pretransplant assessment, the patients' requirements for transplantation need to be categorised in order to rationalise this limited resource. In **fulminant liver failure**, the King's College Criteria are used to predict outcome and the need for OLT (Box 30.1).

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In patients with **cirrhosis**, referral for OLT should be considered once an index complication has occurred, as such events mark a relative reduction in survival rates in the cirrhotic patient. These complications ('decompensations' of chronic disease) include variceal bleeding, onset of ascites or hypoalbuminaemia and development of hepatorenal syndrome. The aim is to bring a patient to transplantation at a point where their expected survival is in the realm of 1–2 years, but before organ failure develops. Calculating the prognosis of patients with cirrhosis is currently defined using both disease-specific and generic clinical tools.

- Child–Turcotte–Pugh score (see Table 2.4) is used most frequently to assess prognosis of cirrhotic patients, establishing three classes of severity (A, B and C).
- Model for End-stage Liver Disease (MELD) score is in current use in the USA. It incorporates values for serum bilirubin, serum creatinine and INR for prothrombin time in a log-transformed equation to estimate likelihood of 3-month survival (Table 2.6). The formula is available at http://www.mayoclinic.org/gi-rst/mayomodel5.html
- A Child–Turcotte–Pugh Score of 7, a MELD score of 10 or any complication of portal hypertension is an appropriate indication for transplant evaluation.

Referral for pretransplant assessment is then made in discussion with the transplant team. The pretransplant assessment ensures the patient will be able to tolerate the stress of the surgery, immunosuppression and highly demanding post-

Box 30.1 King's College Criteria for acute liver failure.

Patients with paracetamol toxicity

- pH <7.3 or
- PT >100 s and serum creatinine level > 300 µmol/l (>3.4 mg/dl) if in Grade III or IV encephalopathy

Other patients

Three of the following variables:

- Age <10 years or >40 years
- Cause:
  - Non-A, non-B hepatitis
  - Halothane hepatitis
  - Idiosyncratic drug reaction
- Duration of jaundice before encephalopathy >7 days
- PT >50 s
- Serum bilirubin >300 µmol/l (>17.6 mg/dl)

transplant care. It includes an extensive cardiopulmonary and psychosocial evaluation, screening for occult infection and neoplasia, as well as careful education of the patient and family.

The operation

The operation to transplant a liver consists of three phases:

1. Removal of the donor liver;
2. Removal of the recipient's native liver;
3. Grafting of the transplant.

- Two main types of incision are used: the 'Mercedes incision' which consists of bilateral subcostal incisions with a midline extension, and the inverted J incision.
- A temporary shunt between the portal system and inferior vena cava is formed in order to reduce the haemodynamic changes that would occur if the hepatic vessels were simply clamped during removal of the native liver.
- Liver is then isolated from the arterial and biliary systems, and removed
- All dissected vessels are prepared for subsequent anastomosis and the donor liver is finally grafted into the site of the native liver.

Postoperative care

Immunosuppression

Immunosuppression in OLT has three main phases: induction, maintenance and treatment of rejection episodes.

Induction

- Typically high-dose steroids along with introduction of a calcinerin inhibitor, either cyclosporin or tacrolimus.
- Common side-effects of the immunosuppressants used are listed in Table 30.1.
- Mycophenolate mofetil or azathioprine may be used as adjuvant agents to allow lower doses of the calcineurin inhibitors.

Protection of renal function is especially important in the early post-transplant period.

Acute cellular rejection (ACR) develops in approximately 70% of liver transplant recipients, typically 5–14 days following transplantation (although it may present later). Treatment of ACR early in the post-transplant period is with intravenous corticosteroids tapered rapidly over several days. ACR not responsive to steroids can be treated by the addition of mycophenolate mofetil and higher levels of tacrolimus.

Maintenance

- In the majority of cases, immunosuppression is with a calcineurin inhibitor (ciclosporin or tacrolimus) started immediately postoperatively with corticosteroids.
- Steroids are slowly reduced and often withdrawn within 6–12 months of OLT, the exception being with autoimmune liver disease.

Chronic rejection occurs late in the post-OLT course and is characterised by vanishing bile ducts (ductopenia). It may respond to a higher dose of tacrolimus, but can lead to the need for retransplantation.

Early post-transplant care

- Admission to the intensive care unit postoperatively:
  - All patients have markedly abnormal aminotransferase, bilirubin and INR in the initial 48–72 h, usually returning to normal

Table 30.1 Mechanism of action and adverse effects of orthotopic liver transplantation immunosuppressive drugs.

Drug	Tacrolimus	Ciclosporin	Prednisone	Mycophenolate mofetil (MMF)	Azathioprine
Mechanism	Calcineurin inhibitors: bind to intracellular proteins, inhibiting the phosphatase activity of calcineurin, resulting in inhibition of gene transcription for the synthesis of lymphokines such as IL-2		Inhibits transcription of IL-1 and IL-6 Blocks antigen recognition Causes redistribution of lymphocytes	Inhibitor of inosine monophosphate dehydrogenase	Inhibitor of DNA and RNA synthesis
Use	Most commonly used immunosuppressants in induction and maintenance Methylprednisone IV is the mainstay of initial treatment of acute cellular reaction (ACR)			Used as adjuvant agents in order to allow lower doses of the calcineurin inhibitors (and hence reduce toxicity) MMF used in steroid-resistant ACR	
Toxicity	Nephrotoxicity Tremor Hypertension Headache GI symptoms Alopecia Diabetes	Nephrotoxicity Tremor Hypertension Headache Hirsutism Gingival hyperplasia	Osteoporosis Osteonecrosis Diabetes Hyperlipidaemia Hirsutism Hypertension Cushingoid habitus	Leukopenia Nausea and vomiting Diarrhoea	Haematological pancreatitis Cholestatic jaundice Hepatitis Interstitial pneumonitis

within a few weeks. This is a result of insults to the graft, such as the ischaemia, which occurs following harvesting, the preservation in transit and the subsequent reperfusion of the graft;
  - If the above indices are rising rather than falling in the early postoperative phase, hepatic artery thrombosis must be excluded by Doppler ultrasound. Primary non-function of the graft may occur and mandates urgent retransplantation.
- After 1 week:
  - ACR becomes an important and frequent cause of increases in the LFTs. It is confirmed by liver biopsy and treated as described above;
  - Nosocomial infectious complications may occur. Fungal infections are of particular concern and are associated with poor prognosis;
  - Toxic effects of the calcineurin inhibitors (early neurological dysfunction, renal impairment and hyperglycaemia) may become evident.
- Following discharge, patients remain under weekly monitoring for the first month. In this phase ACR continues to be a concern, prompting urgent liver biopsy if liver dysfunction recurs.
- Peak onset of action by the calcineurin inhibitors is at 1 month, which is when post-transplant and opportunistic infections can intervene:
  - These include cytomegalovirus, herpes simplex virus, *Pneumocysitis carinii* pneumonia and toxoplasmosis. The use of prophylactic antimicrobials depends on the risk profile of the individual patient and donor in combination;
  - Early recurrence of HCV and HBV can occur at this time. In the case of HBV, prophylaxis with hepatitis B immunoglobulin (with or without antiviral treatment) is effective.

Long-term care

The long-term care of the liver transplant recipient increasingly involves the primary and secondary care teams. Patients post-OLT are at risk of conditions specifically related to immunosuppression and the underlying liver condition. The common complications and their monitoring and management are summarised in Table 30.2.

Malignancies after OLT are more frequent than in the general population. This relates to high-risk behaviour before transplant, specifically cigarette

Table 30.2 Pathogenesis and management of postorthotopic liver transplantation (OLT) complications.

	Pathogenesis	Monitoring	Management
Hypertension	Calcineurin inhibitors (CNI): reversible, dose-dependent hypertension due to vasoconstriction of afferent renal arterioles Corticosteroids: partial mineralocorticoid agonism, expanding plasma volume	Regular medical review, including blood pressure measurement	Lifestyle modifications: • Weight loss • Sodium restriction • Smoking cessation • Exercise • Abstinence from alcohol Wean-off corticosteroids, or reduce CNI dose Medication if persistent: • First-line: calcium-channel blockers: amlodipine and nifedepine (nicardipine, verapamil and diltiazem, increase CNI levels) • Second-line: clonidine, beta-blockers, ACE inhibitors
Renal dysfunction	Pre-existing in substantial minority of cirrhotic patients Glomerular filtration rate (GFR) drops to 60% of baseline within 6 weeks of surgery Causes: • CNIs are major cause • Underlying kidney disease • Ischaemic injury • Diabetes mellitus • Hypertension • Other nephrotoxic drugs • HCV	Routine testing of renal function at review	Treat hypertension and diabetes aggressively Reduce CNI dose (addition of mycofenolate mofetil or sirolimus) Mortality of OLT recipients maintained on dialysis is high and renal transplantation should be considered

(*continued*)

Table 30.2 Pathogenesis and management of postorthotopic liver transplantation (OLT) complications (*continued*)

	Pathogenesis	Monitoring	Management
Post-transplant diabetes mellitus	Affects 10–30% of OLT recipients in first postoperative year Abates with time as doses of corticosteroids and TAC are tapered Insulin resistance final common pathway Exacerbated by: • Corticosteroids • Obesity • CNIs, (direct toxicity on pancreatic beta-cells) • HCV	Screening immediately post-transplant and regularly thereafter with fasting plasma glucose Once diagnosed: • Regular self-monitoring of blood glucose • Management of dyslipidaemia • Screen annually for diabetic complications	Steroid and TAC-sparing regimens in diabetes prior to OLT Lifestyle and immunosuppressive regimen modification Majority require treatment with an oral agent Oral combination therapy followed by oral agent and insulin instituted in a stepwise fashion if needed
Hyperlipidaemia	Prevalence 40–66% CNIs may cause hyperlipidaemia (CYA and, to a lesser extent, TAC) SIR contributes to hypertriglyceridaemia in association with diabetes Risk factors: • High cholesterol pre- OLT • Post-OLT renal dysfunction Metabolic syndrome: genetics, diet, obesity and diabetes	Lipid panel: • Early after transplantation • After any change in immunosuppression	Primary target = correction of LDL cholesterol Lifestyle changes: (alone rarely result in sufficient improvement): • Smoking cessation • Exercise • Dietary modification Contributing medications: • Thiazide diuretics • Beta-blockers • Immunosuppressive agents Early post-OLT usually does not require medication and resolves with reduction in steroids Medical management if lifestyle management and alteration of medications unsuccessful: Isolated hypercholesterolaemia or mixed hyperlipidaemia: HMG-CoA reductase inhibitors ('statins') treatment of choice (*Note*: metabolism of most statins is decreased by CYA) • Hypertriglyceridaemia: Less severe cases managed with fish oil supplements Refractory cases can be safely treated with a fibrate Consider changing SIR to CYA or TAC

Bone marrow disease (BMD)	BMD in cirrhotic patients is low: • Hypogonadism • Malnutrition • Physical inactivity BMD declines after OLT: • Immunosuppressives cause increased resorption as well as decreased formation of bone • Bed rest • Corticosteroids Risk factors: • Most important is low BMD pre- OLT • Older age, • Degree of immunosuppression • Graft dysfunction • Female sex • Lower BMI • Renal dysfunction • Postmenopausal state	Bone densitometry prior to OLT if cirrhotic or other risk factor for osteoporosis Counselling about: • Adequate vitamin D and calcium intake • Weight-bearing exercise • Nutritional repletion • Alcohol use • Smoking cessation	Consider postmenopausal women and men with evidence of hypogonadism for hormone replacement therapy Antiresorptive agents, such as bisphosphonates, are the treatment of choice when osteoporosis diagnosed or long-term steroids predicted

SIR, sirolimus; TAC, tacrolimus; CYA, ciclosporin.

Table 30.3 Postorthotic liver transplantation (OLT) cancer complications.

Cancer type	Association with OLT	Recommended surveillance
Non-melanoma skin cancer	20-fold higher risk than population Most common malignancy in adult OLT recipients Squamous cell carcinomas outnumber basal cell carcinomas	Routine examinations by a dermatologist if: • Sun-damaged skin • Previous history of skin neoplasms • Countries with high ultraviolet light exposure
Colon cancer		Colonoscopic surveillance for all OLT recipients Interval of examination individualised: • 5-year examinations if no previous history of colonic neoplasia • More frequent examinations for higher-risk patients with previous polyps • Ulcerative colitis transplanted for primary sclerosing cholangitis: yearly surveillance
Carcinoma of the oropharynx and oesophagus		Consider routine upper endoscopy and oropharyngeal examination Any new symptom should prompt thorough examination Consider endoscopic surveillance of patients with Barrett's oesophagus
Lung cancer	Particularly increased in alcoholic liver disease (probably related to high rate of smoking)	Consider for screening chest imaging, such as with low-radiation dose chest CT scanning
Post-transplant lymphoproliferative disease	30–50 times risk in general population Usually driven by Epstein–Barr virus	
Recurrence and progression of malignant and premalignant conditions after OLT	Varies greatly with tumour type: • Gynaecological and testicular cancers seldom recur after OLT (<10%) • Prostate, colon and lymphomas recur in 10–20% • Breast, bladder and skin carcinoma recur in 20–50%	Dependent on individual cancer

and alcohol abuse, and chronic immunosuppression, although neither the degree of immunosuppression nor the specific immunosuppressive regimen after OLT has been associated with an increased risk of cancer (Table 30.3).

Strategies to maximise donor pool

The number of donor livers available each year is far fewer than the number of patients listed for liver transplant. This results in significant morbidity and mortality in patients listed and awaiting transplantation. Novel surgical techniques under development to maximise donor organ access include split cadaveric liver and living donor transplantation.

Gastrointestinal history check-list

Dysphagia	**Duration** (months = malignancy)
	Progressive (malignancy or benign stricture) or **intermittent** (other causes)
	Worse with liquids (functional, dysmotility), **solids** (benign or malignant stricture, webs), or **both** (dysmotility, neurological cause)
	Timing in relation to swallow (instant = pharyngeal or neuromuscular causes, or few seconds later)
	Nasal aspiration (pharyngeal or neuromuscular causes)
	Cough (nocturnal = dysmotility; instantly after swallowing = pharyngeal or neuromuscular causes)
	Weight loss (malignancy >> benign stricture, dysmotility)
	Associated features (e.g. systemic sclerosis, neurological disorders, past history of reflux suggesting benign stricture)
Abdominal pain	**Onset** (sudden = vascular/infection/obstruction; gradual = inflammatory/neoplastic/functional)
	Frequency/duration (intermittent *vs.* constant)
	Location, radiation or referral (visceral poorly localised/somatic well localised, radiation and referral pattern may define organ involved)
	Character and nature (may define organ involved)
	Exacerbating and relieving features (association with food – timing/type of food, relief with passage of flatus = rectal sensitivity, effect of different medicines, stress)
	Associated symptoms (bowel habit, vomiting, abdominal distension, haematuria, haematochezia, haematemesis, malaena, weight loss, fevers)
GI bleed	**Haematemesis** (cause proximal to jejunum)
	Melaena (cause usually proximal to left colon)
	Visibly red blood loss (distal colon)
	On tissue only (anal disease)
	Associated mucus (IBD, colorectal cancer, villous adenoma, solitary rectal ulcer syndrome)
	Abdominal pain (see above)
	Signs of chronic liver disease (varices)
	Signs of circulatory compromise (varices)
	Fever, sweating (Crohn's disease, intra-abdominal TB, infectious gastroenteritis)
	Drug history (especially NSAIDs, anticoagulants, alcohol, smoking)
	Weight loss (malignancy)

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Diarrhoea	**Watery** (secretory small intestinal causes – infectious or neoplastic – or microscopic colitis), **steatorrhoea-like** (pancreatic or small intestinal disease) or **other**
	Nocturnal diarrhoea (organic cause) or **daytime only** (IBS)
	Weight loss (malignancy > IBD, malabsorption, hyperthyroidism)
	Relationship to pain (eased by bowel opening = diverticular disease, IBD stricture or IBS; unrelated = ischaemic colitis, drug-induced, hypolactasia)
	Family history (IBD, coeliac disease, colorectal cancer)
	Drug history (especially antibiotics, iron, NSAIDs, PPIs)
	Recent travel (infectious diarrhoea)
	Past history (surgical, radiation, systemic disease)
	Incontinence (complication of diarrhoea)
Constipation	**Urge frequency** (daily = normal transit; less than daily = slow transit)
	Bowel frequency (to confirm constipation)
	Stool consistency (to confirm constipation)
	Rectal evacuation difficulty (need to strain, incomplete emptying, perineal or anal digitation – all suggest pelvic floor dysfunction)
	Rectal prolapse (a cause and exacerbator of constipation)
	Diet (encourage more fibre in normal transit, avoid excess in slow transit)
	Drug history (especially anticholinergics, iron, opiates; eating behaviour)
	Past history (eating disorder, abdominal surgery (adhesions), pelvic or anal surgery (local pain causing constipation) neurological disorders, hypothyroidism, hypercalcaemia)
Jaundice	**Prehepatic** (haemolytic; unconjugated hyperbilirubinaemia, normal urine, normal stool; reduced serum haptoglobin, features of haemolysis on blood film)
	Hepatic (unconjugated or mixed hyperbilirubinaemia; dark urine, normal stool; acute or chronic liver disease, Gilbert's, neonatal jaundice)
	Posthepatic (obstructive/cholestatic; conjugated hyperbilirubinaemia; dark urine, pale stool, severe itch; extrahepatic [cholelithiasis, head of pancreas mass] *vs*. intrahepatic biliary disease [sclerosing cholangitis, primary biliary cirrhosis])

Abdominal examination routine

1. Approach the patient's right-hand side and introduce yourself
2. Ensure patient is in a good position – lying comfortably on one pillow, with the abdomen exposed
3. General inspection (should take <60 s if examiner does not stop you):
   - Look around the bed (drip stands, diet sheets)
   - Survey the patient (scratch marks, gynaecomastia, reduced body hair)
   - Hands:
     - Clubbing (Crohn's disease, cirrhosis)
     - Dupuytren's contracture (alcoholic liver disease)
     - Palmar erythema (cirrhosis)
     - Leuconychia (cirrhosis, Crohn's disease)
     - Liver flap (examiner may stop you, but you should offer to examine for this)
       Ask patient to extend elbows and cock wrists back towards the face
       Then ask patient to fan fingers out gently
       You are looking for a bird's wing flap at the wrist
   - Eyes:
     - Anaemia – expose lower eyelid
     - Jaundice – look at conjunctiva
   - Lips:
     - Cyanosis (liver disease)
     - Parotid swelling (alcoholic liver disease)
     - Pigmentation (Peutz–Jegher's)
     - Telangiectasia (hereditary haemorrhagic telangiectasia)
     - Ulcers (Crohn's disease)
   - Anterior chest wall:
     - Cervical lymphadenopathy (lymphoma, gastric cancer Virchow's node)
     - Palpate for gynaecomastia
4. Inspect abdomen (should take <15 s, if examiner does not stop you):
   - Prominent abdominal vessels
   - Scars (do not forget nephrectomy scars posteriorly!)
   - Stoma (an ileostomy is generally in the left iliac fossa and smaller than a colostomy which is often – but not always – on the right side)
   - Distension:
     - Generalised (ascites)
     - Localised (upper abdo, periumbilical, suprapubic, flanks, iliac fossae)
   - Pulsation
5. Palpate abdomen:
   - Enquire about areas of pain
   - Assess direction of flow (best assessed in veins *below* umbilicus):
     - Cranially in inferior vena cava
     - Away from the umbilicus in portal hypertension
   - Superficial palpation in a systematic fashion (traditionally in an anticlockwise spiral from the right iliac fossa, ending in the umbilicus):
     - Use pulps – not tips – of fingers
   - Internal organ palpation:
     - Begin at the right iliac fossa again:
       Liver: work upwards to right upper quadrant
       Spleen: work diagonally to left upper quadrant
     - Next to left and right flank for the kidneys, by bimanual palpation:

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Right hand under patient and left hand on top for left kidney; left hand under patient and right hand on top for right kidney

Keep upper hand still and firmly pressed down, whilst lower hand 'ballotts' the kidney

- *If* any organs are felt:
  - Ask patient to take a deep breath in to assess for movement with respiration
  - Assess edge of the mass – contour, texture
  - Assess if you can 'get above' the mass (kidney)
  - Assess if it is separate to the costal margin (kidney)
- Offer to assess for inguinal lymph nodes and hernia orifices

6. Percuss abdomen – the principle of percussion is to move from resonant to dull:
- Percuss down from lower right chest until upper border of liver dullness is reached, then repeat from lower abdomen upwards
- Repeat the process for the spleen
- Shifting dullness:
  - First check for stony dullness in flanks – if absent (rare), there is gross ascites and no need to continue; alternatively
  - Start percussing in the midline and gradually move laterally to patient's left until the note becomes stony dull; now ask patient to roll on to their right (facing you) and allow 15 s for the fluid to settle before percussing back towards the midline and listening to the note of the dullness that has shifted

7. Auscultate abdomen:
- Offer to listen to:
  - Bowel sounds
  - Liver venous hum (acute hepatitis)
  - Renal artery bruit

8. Complete examination:
- Offer to:
  - Examine external genitalia
  - Undertake a rectal examination
  - Stool

Rectal examination routine

1. Try to put patient at ease, and explain the procedure
2. Place patient in left lateral position (underwear off or at knees), with a drape over them
3. Part the buttocks and inspect for:
   - Excoriation
   - External haemorrhoids
   - Anal fissure
   - Skin tags
   - Fistulous openings
   - Anal warts
4. Insert a well lubricated finger into the anus, taking note of:
   - Anal tone at rest and on voluntary squeeze
   - Any rectal mass (polyp, cancer, stool)
   - Prostate size and texture in men
5. Withdraw finger and observe the nature of material on the glove
6. Clean the anus, and offer the patient tissues and privacy to dress

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Common OSCE cases

It is essential to look for features of other diseases, to help identify causes.

Hepatomegaly	Common causes: • Cirrhosis • Right heart failure • Lymphoma • Myeloproliferative disorder (i.e. polycythaemia rubra vera, chronic myeloid leukaemia, myelofibrosis) • Malignancy (irregular edge to liver)
Hepatosplenomegaly	If also anaemic, diagnosis may be: • Cirrhosis with portal hypertension • Lymphoma • Myeloproliferative disorder • Tropical disorders (malaria, kala-azar) If lymphadenoapthy present, diagnosis may be: • Chronic lymphocytic leukaemia • Lymphoma
Splenomegaly	Massive – most commonly: • Myeloproliferative disorder; moderately enlarged – as above • Cirrhosis with portal hypertension • Lymphoma; slightly enlarged – as above • Infections – infectious mononucleosis, infectious hepatitis, bacterial endocarditis
Enlarged kidney(s)	Bilateral: • Polycystic kidney disease • Amyloidosis • Bilateral hydronephrosis Unilateral • Hydronephrosis • Renal carcinoma
Isolated ascites	Usually with features of chronic liver disease or hepatomegaly, but may be isolated. Look for signs of paracentesis and of causes other than liver disease (heart failure, intra-abdominal malignancy, operative scars)
Chronic liver disease	Have a list of causes and complications of cirrhosis at your fingertips

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Self-assessment case studies: Questions

1. **An 18-year-old man with cystic fibrosis has had colicky abdominal pain and the passage of pale loose stools for many months. He presents acutely with a major haematemesis.**
   - **a.** Give two possible causes of his diarrhoea.
   - **b.** Give two possible causes of his abdominal pain.
   - **c.** What is the most likely cause of his haematemesis?

2. **A 35-year-old asymptomatic new blood donor is found to have the following blood results:**

Serum bilirubin	46 µmol/l
Serum alkaline phosphatase	110 IU/l (normal range 50–150)
Serum aspartate transaminase	40 IU/l (normal range 15–55)

   - **a.** Give two possible causes for this.
   - **b.** Can she give blood with these two causes?

3. **A 23-year-old man who is HIV positive complains of severe retrosternal pain and dysphagia, and 2 weeks of bloodless diarrhoea. He has had weight loss of 5 kg in that time.**
   - **a.** Give one viral and one non-viral cause of the chest pain.
   - **b.** Give two causes of diarrhoea.

4. **A 66-year-old retired secretary has been taking warfarin for 15 years (for recurrent DVTs). She presents with a symptomatic anaemia (Hb 0.89 g/l), microcytosis (MCV 67 fl, normal range 76–100 fl) and hypochromia (MCH 20 pg/cell, normal range 26–34 pg/cell). She denied any abdominal pain, alteration of bowel habit, overt blood or weight loss. Examination revealed multiple telangiectasia on the lips and hands, but was otherwise entirely normal.**
   - **a.** What is the likeliest haematological explanation for her symptoms and what investigations would confirm this diagnosis?
   - **b.** What investigations are mandatory to find the cause of your answer to (a)?
   - **c.** What are the two likeliest possible causes of her anaemia that need excluding by your answer in (b)?

5. **An 83-year-old woman presented with a 3-day history of worsening diarrhoea starting 5 days after discharge from hospital (she had been admitted for pneumonia). Her bowels were opening 10–15 times by day and night, passing watery stool without blood. On examination, she had a temperature of 37.8° C with a pulse of 96 beats/min and a blood pressure of 110/58 mmHg. Her chest was clear, and her abdomen was soft but diffusely tender.**
   - **a.** Give a differential diagnosis of three conditions.

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b. What tests would confirm the likeliest diagnosis?
c. Following resuscitation, what treatment should she be started on?

6. **A 59-year-old woman presents with asymptomatic liver test abnormalities\; bilirubin 8, ALP 325, ALT 122, GGT 637, AST 68. Her only medication is 150 mg Aspirin daily. There is no history of transfusions, tattoos, piercings or intravenous drug use. She takes no alcohol. There is no family history of liver disease. Her past medical history includes open cholecystectomy.**

Examination reveals no stigmata of chronic liver disease and no abdominal masses or organomegaly. Serum biochemistry, FBC and viral serology are negative. However there is hypergammaglobulinaemia with an ANA titre > 1:5120. SMA, AMA, LKM1 are negative. Liver biopsy shows interface hepatitis with abundant plasma cells. Treatment with prednisone 40 mg daily is initiated and over the subsequent 4 weeks the liver tests return to the normal range.

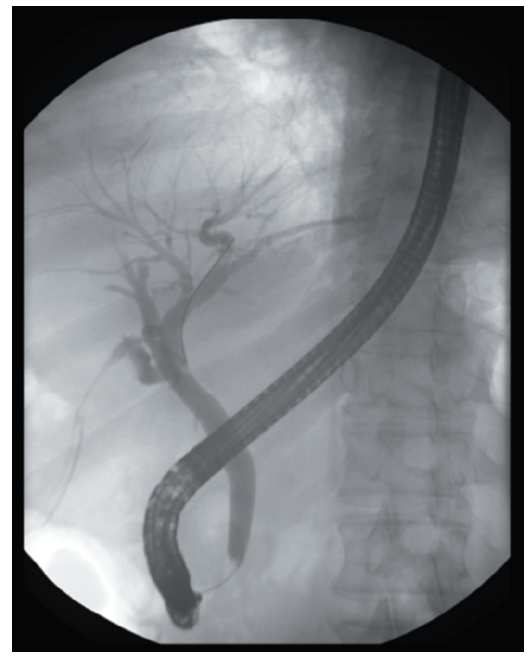
a. What is the likeliest diagnosis?
b. What drug might be used as a steroid-sparing agent?
c. What drugs are implicated in the aetiology of this condition?

7. **A 60-year-old woman presented with a 1-year history of intermittent dysphagia, which was gradually worsening. This was occurring for both solid and liquid meals, and it was taking her longer to manage her meals. She was often woken from sleep with paroxysms of coughing. She had lost 3 kg in weight. She was taking omeprazole for long-standing, well-controlled reflux.**

a. What is the likeliest diagnosis, and give a differential of two other possibilities?
b. What investigation is required to confirm the diagnosis?

8. **A 41-year-old woman underwent laparoscopic cholecystectomy that had to be converted to an open procedure because of difficulty identifying the cystic duct. A percutaneous drain was left in the gallbladder fossa.**

Post cholecystectomy she is troubled by abdominal pain and has not passed flatus by day 3. Chest X-ray shows a small amount of free subdiaphragmatic gas on the right side. Abdominal X-ray shows multiple air fluid level in mildly dilated small bowel. CT of the abdomen demonstrates the above findings and also a focal fluid collection in the gallbladder fossa. ERCP is undertaken and the resultant cholangiogram is shown.



a. What does the ERCP demonstrate?
b. At presentation what was the risk to this patient of complications related to her cholelithiasis and how does this compare to the risk of cholecystectomy?
c. In consenting this patient for laparoscopic cholecystectomy, what risks should the surgeon have stated and what is the expected rate of conversion to open cholecystectomy?
d. How should this patient now be treated?

Self-assessment case studies: Answers

1. **Gastrointestinal sequelae of cystic fibrosis**
   - **a.** This is steatorrhoea – the possibilities are that it is due to pancreatic insufficiency secondary to chronic pancreatitis (one of the sequelae of cystic fibrosis) or small bowel bacterial overgrowth (also one of the sequelae of cystic fibrosis).
   - **b.** The abdominal pain may be secondary to chronic pancreatitis or gallstones – both of which are more common in cystic fibrosis. In addition, incompletely digested food may lead to bolus small intestinal obstruction.
   - **c.** Oesophageal variceal bleeding – secondary to the cirrhosis that complicates cystic fibrosis – would explain the haematemesis.

2. **Isolated elevated bilirubin in an asymptomatic patient**
   - **a.** Possible causes are Gilbert's syndrome (likeliest) or asymptomatic carriage of hepatitis C.
   - **b.** Blood donation is acceptable with the former, but not the latter.

3. **Causes of gastrointestinal infection in an HIV-positive patient**
   - **a.** Herpes simplex, cytomegalovirus, candida.
   - **b.** Cytomegalovirus, cryptosporidium, giardiasis and any cause of bacterial gastroenteritis is more common in AIDS patients.

4. **Microcytic hypochromic anaemia**
   - **a.** Likeliest cause is iron-deficiency anaemia, confirmed by serum iron studies (serum iron and iron-binding capacity). There is no history of chronic illness to raise the possibility of the 'anaemia of chronic disease'.
   - **b.** Upper GI endoscopy and colonoscopy.
   - **c.** Colorectal cancer (often asymptomatic) and hereditary haemorrhagic telangiectasia (in view of the cutaneous and oral telangiectasia).

5. **Diarrhoea after antibiotics**
   - **a.** The differential includes *Clostridium difficile* infection, antibiotic-induced diarrhoea, an unrelated coincidental condition (colorectal cancer, ulcerative colitis, infective gastroenteritis).
   - **b.** Stool test for *Clostridium difficile* toxins A and B is preferred to a flexible sigmoidoscopy.
   - **c.** Start oral metronidazole or vancomycin.

6. **Autoimmune hepatitis**
   - **a.** The diagnostic scoring system for AIH includes scores for gender, ALP:AST ratio, IgG, ANA, viral markers, drugs, alcohol, concurrent immune disease, histological features, HLA status and treatment response.

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b. Azathioprine is commonly used as a steroid-sparing agent in AIH.
c. Oxyphenisatin, nitrofurantoin, minocycline, alpha-methyldopa and clometacine have been implicated.

7. **Intermittent dysphagia with moderate weight loss**
   a. Achalasia is the most likely diagnosis. With dysphagia to both liquids and solids, over such a long time, the possibility of carcinoma of the oesophagus and benign oesophageal stricture are less likely.
   b. The diagnostic investigation of choice is oesophageal manometry, not barium swallow or upper GI endoscopy (which are important to exclude the differential).

8. **Iatrogenic biliary leak**
   a. The ERCP demonstrates leakage of contrast from the cystic duct stump. This is the cause of the local fluid collection in the gallbladder fossa.
   b. The risk of complications in a patient with typical colicky pain and gallstones is about 1–2%, as compared to 0.1–0.2% in asymptomatic patients. Open cholecystectomy is safe and effective with an overall mortality of 0.1–0.5%.
   c. Patients undergoing laparoscopic cholecystectomy should be consented for the risks of anaesthesia as well as specific risks of the procedure, including bleeding, need for further intervention to remove stones outside the gallbladder, damage to the bile ducts, infection and abscess formation, problems with wound healing, the possibility of persistent biliary-type pain, and the need to convert to open cholecystectomy. The frequency of this is widely quoted as 5%.
   d. This patient should now have endoscopic sphincterotomy and/or biliary stent placement to ensure adequate bile drainage via the ampulla. She may then be managed conservatively with antibiotics and analgesia. If an abscess forms, it will require radiologically guided or surgical drainage.

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