GASTROENTEROLOGY AND HEPATOLOGY

Lecture Notes

Stephen Inns
Anton Emmanuel

2nd Edition

WILEY Blackwell

Gastroenterology and Hepatology

Lecture Notes

This new edition is also available as an e-book. For more details, please see www.wiley.com/buy/9781118728123 or scan this QR code:

Gastroenterology and Hepatology
Lecture Notes

Stephen Inns

MBChB FRACP
Senior Lecturer
Clinical Lecturer in Gastroenterology
Otago School of Medicine, Wellington
Consultant Gastroenterologist
Hutt Valley Hospital, Wellington
New Zealand

Anton Emmanuel

BSc MD FRCP
Senior Lecturer in Neurogastroenterology
and Consultant Gastroenterologist
University College Hospital
London, UK

Second Edition

WILEY Blackwell

Contents

Part IV Study Aids and Revision

Part V Self-Assessment: Answers

Key to the important aspects icons

Key clinical point

Emerging topic

Important basic science point

Preface to the second edition

He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.

William Osler 1849–1919

Let the young know they will never find a more interesting, more instructive book than the patient himself.

Giorgio Baglivi 1668–1707

With the first edition of *Lecture notes in Gastroenterology and Hepatology* we strove to create a book that read just as we teach, incorporating the important and pertinent parts of anatomy, physiology and pathology into the structure of the lesson. In this way the building blocks of clinical understanding can illuminate rather than distract, or worse yet bore, the student or aspiring gastroenterologist. With this edition we have attempted to augment and clarify this concept by using a very uniform structure. Each section, where it is at all appropriate, is divided into subsections on the epidemiology, causes, clinical features, investigation, treatment and prognosis of the condition being considered. We hope this will help with understanding the material and integrating it into practice, as well as improve the textbook as a reference source or revision aid. Icons that alert the reader to those aspects of a disease that we believe are especially important, whether it be from a basic science, clinical or emerging topic perspective, have been added to focus the reader further.

This textbook is intended as a source of information and advice for all who are starting out in the important work of assisting people with disturbances of gastroenterological and hepatological function, from the most junior of medical students to those preparing for specialist exams. To this end we have added 'key point' summaries to each chapter, as an aid to revision and understanding. We have also added an extensive 'best answer' multi-choice question section, in the style of the MRCP and FRACP examinations. These questions remain very clinically focused and draw heavily on our own clinical experiences. We believe that those early in their training will find them just as illuminating as those further along will find them challenging. Additionally, we have added further line diagrams and clinical images, with the aim of illustrating the important concepts without cluttering the book.

We firmly believe that our patients are the people who teach us the most. However, guidance from our colleagues and sources such as this book help light the path that each of us must walk to become the best clinician we can. We hope this book guides you in the same way that writing it has us.

Stephen Inns and Anton Emmanuel

Preface to the first edition

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

Hippocrates 460–357 BCE

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 1809–94

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 on 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.

Anton Emmanuel and Stephen Inns

About the companion website

Gastroenterology and Hepatology Lecture Notes is accompanied by a companion website, featuring 16 in-depth case studies:

www.lecturenoteseries.com/gastroenterology

Part I

Clinical Basics

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. The underlying diagnoses and pathological mechanisms encountered in chronic pain are often quite different from those seen in acute pain, and for this reason each is considered in turn here.

Chronic abdominal pain

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 1.1). 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).

Referred pain occurs due to the 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 pain from a ruptured spleen or pancreatitis.

Clinical features

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 or enquiries 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 1.2). These are indicators that increase the likelihood that an organic condition underlies the pain. The alarm features guide further investigation.

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

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 is more likely to be gradual in onset.

Box 1.1 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

Box 1.2 Alarm features precluding a diagnosis of irritable 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 1.3 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

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 1.3).
- **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 very longstanding pain is unlikely to be related to malignant pathology.

Location: Radiation or referral (Figure 1.1 right)

- **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).
- **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 (Figure 1.1 left) 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.
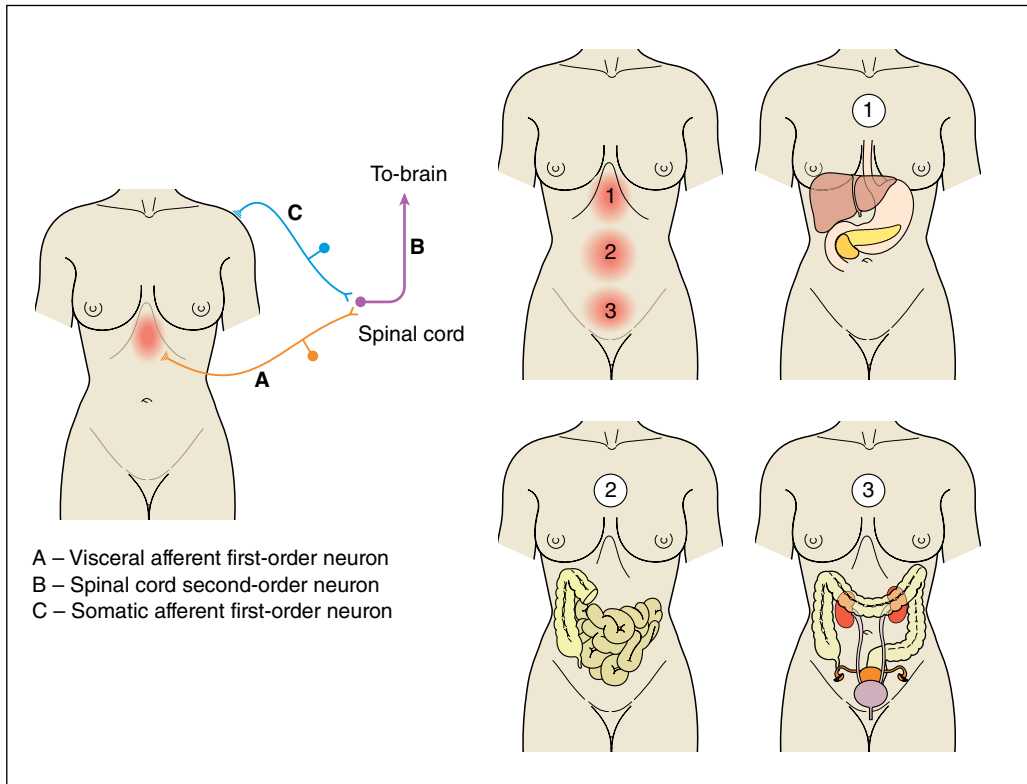
Figure 1.1 *Left*: Mechanism of referred pain. *Right*: Location of pain in relation to organic pathology. Source: Frederick H. Millham, in Feldman M, Friedman L, Brandt L (eds) (2010) *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th edn, Philadelphia, PA: Saunders, Figure 10.1. Reproduced with permission of Elsevier.

- **Sharp, pricking?** Somatic pain: originates from the abdominal wall or parietal peritoneum (Box 1.1).

One process can cause both features, the classic 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.
- **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 when 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 are 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 yellowing in jaundice, or periorbital corneal arcus 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 that a patient is at risk for intestinal ischaemia; congestive heart failure is

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

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 gastrointestinal (GI) system per se begins with careful inspection of the mouth with the aid of 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 lymphadenopathy.
- **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 ask first whether 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. While 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.

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) is/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 full blood count (FBC); urea, creatinine and electrolytes; liver function tests (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 1.1).

CLINICAL EXAMPLE 1.1

HISTORY 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 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 mucus. 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 minutes to some hours at a time. There is no position in which she can get comfortable 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.

EXAMINATION Observation reveals a thin woman with no hand or face signs of gastrointestinal 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 and investigation plan, one must first consider which organ(s) might be involved, then what the possible pathologies in those organs might be, before considering the investigations that are useful for each possible pathology in each organ system. This will allow a tailored approach to directed investigation that is cost-effective and limits the potential harm to the patient.

Likely organ involved 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.

Likely pathology The most likely diagnoses in this setting are inflammatory bowel disease and functional GI disease (IBS). Most patients with gastrointestinal symptoms require serological testing for coeliac disease, as it is very common and its symptoms commonly mimic other diseases. 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, although unlikely in a young woman, intestinal ischaemia. Less likely causes in other organ systems include biliary colic, ovarian pain and renal colic.

Investigation plan 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 computed tomography (CT) or magnetic resonance imaging (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.

Acute abdominal pain

The patient presenting with acute abdominal pain is 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 constitute 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, who therefore warrant more expeditious evaluation and treatment.

Clinical features
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. The 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.

Table 1.2 Approach to differential diagnosis and directed investigation for Ms AP.

Likely organ involved	Likely pathology	Investigation choices	Investigation plan
Small bowel and colon	Inflammatory bowel disease	Ileocolonoscopy CT/MRI enterography US small bowel Capsule endoscopy	Stool test Ileocolonoscopy CT (or MRI) enterography
	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	
	Neoplasia	Ileocolonoscopy and enterography (CT/MRI) or capsule endoscopy	
	Ischaemia	Angiography	
Biliary system	Biliary stones, neoplasia	Ultrasound abdomen MRCP Endoscopic ultrasound 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.

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 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 non-steroidal anti-inflammatory drugs (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 indications 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.

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 'take 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)

- **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.
  - 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 overactive 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.

Investigation

Most patients will have an 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

Diffuse abdominal pain

Acute pancreatitis   Mesenteric ischaemia
Diabetic ketoacidosis   Peritonitis (any cause)
Early appendicitis   Sickle cell crisis
Gastroenteritis   Spontaneous peritonitis
Intestinal obstruction Typhoid fever

Right or left upper quadrant pain

Acute pancreatitis
Herpes zoster
Lower lobe pneumonia
Myocardial ischaemia
Radiculitis

Right upper quadrant pain

Cholecystitis and biliary colic
Congestive hepatomegally
Hepatitis or hepatic abscess
Perforated duodenal ulcer
Retrocecal appendicitis (rarely)

Left upper quadrant pain

Gastritis
Splenic disorders (abscess, rupture)

Right lower quadrant pain

Appendicitis
Caecal diverticulitis
Meckel's diverticulitis
Mesenteric adenitis

Left lower quadrant pain

Sigmoid diverticulitis

Right or left lower quadrant pain

Abdominal or psoas abscess   Mittelschmerz
Abdominal wall haematoma   Pelvic inflammatory disease
Cystitis   Renal stone
Endometriosis   Ruptured abdominal aortic aneurysm
Incarcerated or strangulated hernia Ruptured ectopic pregnancy
Inflammatory bowel disease   Torsion of ovarian cyst or teste

Figure 1.2 Likely pathologies according to location of acute pain. Source: Frederick H. Millham, in Feldman M, Friedman L, Brandt L (eds) (2010) *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th edn, Philadelphia, PA: Saunders, Figure 10.3. Reproduced with permission of Elsevier.

gallbladder, and gynaecological and obstetric conditions. CT has emerged as the dominant imaging tool for evaluation of the patient with severe acute abdominal pain. 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 have been shown to reduce the need for exploratory laparotomy and hence morbidity, mortality and medical expense.

Management and prognosis

The management and prognosis of both acute and chronic abdominal pain very much depend on the underlying cause. The management and prognosis of the individual diseases that cause abdominal pain (see Box 1.3 and Figure 1.2) are dealt with in each of the individual disease chapters of this book (Chapters 7 to 30).

KEY POINTS

- Peritoneal pain localizes to the area affected, whereas visceral pain tends to be felt in the upper abdomen – foregut; central abdomen – midgut; or lower abdomen – hindgut.
- Mode of onset, time course, location and radiation, character and exacerbants/relievers are essential to determining the cause of abdominal pain.

- Symptoms associated with the pain are invaluable in further localising the disease process.
- Develop a wide-ranging list of differential diagnoses first, then tailor the investigative strategy to that list and other factors that affect the individual patient.

SELF-ASSESSMENT QUESTION

(The answer to this question is given on p. 265)

A 45-year-old woman presents acutely with vague, cramping, right upper quadrant, epigastric and right shoulder blade pain. She has experienced similar pain on a few previous occasions over the last year, but never this severe. In the past the pain has been exacerbated by fatty meals, as on this occasion. She cannot get comfortable with the pain; it tends to come in waves but never completely abates. When it is present she finds breathing more difficult. She has taken paracetamol with minimal relief.

With regard to your initial approach to this patient, which of the following is most true?

(a) The localisation of her pain to one area indicates that there is irritation of the parietal peritoneum.

(b) Her scapular pain indicates that there is retroperitoneal involvement.

(c) Her description of the pain makes a hollow organ the likely source.

(d) The epigastric and right upper quadrant location of her pain indicate that it is likely to be coming from the midgut.

(e) She is describing radiation of the pain to the back, which makes a pancreatic cause more likely.

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.

Epidemiology

The exact epidemiology of hepatic disease in the world is largely unknown. However, most estimates show that it is increasing out of proportion to many other chronic diseases. This is largely driven by increasing rates of obesity and non-alcoholic fatty liver disease, as well as of alcohol consumption and hepatitis B and C. Some sense of the burden of disease is given by the rates of cirrhosis and liver cancer, as they represent the end stage of liver pathology. Even across Europe the incidence of cirrhosis varies widely, with 1 in 1000 Hungarian males dying of cirrhosis each year compared with 1 in 100,000 Greek females. The World Health Organization (WHO) estimates that liver cancer is responsible for around 47,000 deaths per year in the European Union (EU).

Clinical features

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 those in the following sections.

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? (NB: Antibiotic-related disease may take up to two weeks to present)
  ○ 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?

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 pruritus 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.

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

- 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 (see Chapter 29).
- 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 present uncommonly 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 a 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, and identifying aetiology and decompensation.

- **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

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 (haemochromatosis)	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 (non-alcoholic fatty liver disease)	
Testicular atrophy	Diffuse lymphadenopathy (lymphoproliferative disease)	

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

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 indicate 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 that it is due to ascitic fluid shift.

Investigation

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 these 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. These would commonly include:

- Hepatitis A, B and C serology.
- Autoimmune screen to include antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), smooth muscle antibodies (SMA) and liver/kidney microsomal antibody type 1 in the younger patient.
- Serum immunoglobulin (Ig) 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.

> **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
> - Prior to liver transplant to assess donor

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.

Because of the risk from liver biopsy (1 in 100 risk of bleeding or perforation), non-invasive means of determining the degree of liver damage (fibrosis) have been developed, in order to predict prognosis and guide treatment for diseases such as Hepatitis B and C. One such tool is the Fibroscan®. This uses a mechanical pulse, generated at the skin surface and propagated through the liver. The velocity of the wave generated is measured by ultrasound and directly correlates with the stiffness of the liver: the stiffer the liver, the greater the degree of fibrosis.

Assessment of the severity of liver disease

Where chronic liver disease is confirmed, some assessment of the severity of hepatic dysfunction should be made. The commonest scoring system used is the Child–Turcotte–Pugh score (Table 2.4).

This score is calculated using the total bilirubin, serum albumin, international normalised ratio (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–Turcotte–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 is the Model for End-stage Liver Disease (MELD) score (Table 2.6).

Table 2.4 Child–Turcotte–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)

INR, international normalised ratio.

Table 2.5 Prognosis related to Child–Turcotte–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

KEY POINTS

- Jaundice becomes visible when the serum bilirubin is about 35 micromol/L.
- Jaundice in the absence of dark urine suggests unconjugated hyperbilirubinaemia (Gilbert's or haemolysis).
- Pale stool and jaundice may suggest biliary obstruction; the presence of urinary bilirubin (conjugated) in the absence of urinary urobilinogen confirms this.
- A careful medication history is essential – antibiotics particularly can take up to two weeks to cause their effect on the liver.
- The 'signs of chronic liver disease' are most useful for just that – determining whether liver disease is likely to be chronic or not.
- It is useful to have a 'standard hepatitis screen' in mind, including hepatitis B and C (A if acute), ANA, AMA, SMA (LKM1 if young), serum immunoglobulins and EMA/tTG. Also serum copper and caeruloplasmin, ferritin and transferrin, and alpha1 antitrypsin levels in the young or those with a family history of hepatitis.
- Liver biopsy is rarely used for diagnostic purposes and its value in assessing the severity of fibrosis is slowly being replaced by non-invasive alternatives.