PART I

Overview: Clinical Fundamentals of Hepatology

CHAPTER 1

History Taking and Physical Examination for the Patient with Liver Disease

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Key concepts

- The history and physical examination may provide clues to the presence of liver disease in a person thought to be healthy.
- In a patient undergoing evaluation for liver disease, the history and physical examination help determine the underlying cause of liver injury, presence or absence of advanced hepatic fibrosis, and evidence of clinical complications of cirrhosis and portal hypertension.
- Common causes of liver injury in patients with liver disease of unknown cause include nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, hepatitis C, and drug-induced liver injury. The patient should be assessed carefully for excessive alcohol intake, new medication or herbal and dietary supplement use, risk factors for hepatitis C, and evidence of metabolic syndrome.
- In a patient with known liver disease, clinical evaluation for advanced hepatic fibrosis has particular importance, because one third of patients who present for an outpatient hepatology evaluation already have underlying cirrhosis.
- The skin examination is helpful when assessing a patient for advanced hepatic fibrosis; Terry's nails, spider telangiectasias, decreased body hair, gynecomastia, and palmar erythema are associated with cirrhosis with a specificity of 89–97%.
- Assessment of liver span, tenderness, and contour provides important clinical information. Liver span is best assessed by percussion or the "scratch test." In general, the normal liver span is less than 12 cm in the midclavicular line, and the edge is smooth and nontender.
- For the patient with established cirrhosis, careful attention should be paid to vital signs. A reduced mean arterial pressure is associated with renal impairment, particularly when the mean arterial pressure drops below 82 mmHg. Weight gain raises concern for the development of fluid retention and ascites, and weight loss may be associated with malnutrition or malignancy.
- Ascites may be suspected on physical examination by the detection of flank dullness, bulging flanks, shifting dullness, and a fluid wave. Flank dullness and bulging flanks have a sensitivity of at least 80% but a specificity of only 59% for detecting ascites.

The liver is an organ with a broad set of critical biologic functions, a unique dual vascular supply, and several distinct cell types that contribute to its physiologic functions as well as potential pathology. Most of the key functions of the liver are carried out by the hepatocytes, which are the most abundant cell type in the liver. Hepatocytes are responsible for drug detoxification, protein synthesis (including albumin and coagulation factors), excretion of bile for digestion, and synthesis of cholesterol and fatty acids. Injury to hepatocytes and the pursuant inflammation may occur from a toxin-mediated insult such as alcohol or medications, lipotoxicity as seen in fatty liver, infectious causes such as viral hepatitis, or autoimmunity. Stellate cells are less abundant, comprising only about 5% of parenchymal cells and, in health, are the primary site of vitamin A storage. In the setting of chronic inflammation, however, stellate cells are responsible for the deposition of extracellular matrix that leads to cirrhosis. The process of progressive hepatic fibrosis, in general, proceeds over a timeframe of years to decades. This slow progression allows effective intervention if liver disease is identified and treated early in its clinical course. Unfortunately, chronic liver injury is often asymptomatic, and symptoms and signs may not manifest until advanced fibrosis or decompensated liver disease has ensued.

In the evaluation of a patient with liver disease, the focus of history taking and the physical examination will be guided by the reason for which the patient has

Schiff's Diseases of the Liver, Twelfth Edition. Edited by Eugene R. Schiff, Willis C. Maddrey and K. Rajender Reddy.

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presented and has been referred for consultation. Common reasons for referral to a hepatologist include elevated liver biochemical test levels, abnormal serologic test results, jaundice, known chronic liver disease, or evidence of decompensated liver disease. For all of these clinical scenarios, specific historical elements and physical examination findings may provide important insights into the ongoing disease process. In general, the clinician seeks, through history taking and physical examination, to determine the (i) etiology of liver injury, (ii) presence or absence of advanced hepatic fibrosis, and (iii) existence of clinical complications of cirrhosis and portal hypertension. The clinical objectives are to identify the cause of injury and address it early in the disease course to prevent development of advanced hepatic fibrosis, and, if cirrhosis is already present, to monitor the patient carefully for complications of end-stage liver disease.

Abnormal liver biochemical test levels or known liver disease

History taking

Acute and chronic liver injury has a broad spectrum of clinical presentations, and patients present to medical attention for a wide variety of reasons. Many patients are completely asymptomatic and come to medical attention after a routine physical examination or life insurance testing has demonstrated elevated liver biochemical test levels. Others, particularly those with acute hepatitis, may present with abdominal pain, nausea and vomiting, fever, or jaundice. The duration of liver injury, particularly in the absence of symptoms, is not always certain. Clues such as the time of onset of symptoms, prior normal test results, and the presence of potential risk factors may help differentiate acute injury from chronic liver disease.

When evaluating a patient with abnormal serologic test results or a known history of a specific liver disease, the focus of history taking and the physical examination is both to provide clues toward the underlying etiology of liver injury (if unknown) and to assess the patient for clinical evidence of advanced hepatic fibrosis. Central to this objective is an understanding of the most common causes of liver injury and chronic liver disease. A cohort of 1040 patients in the Chronic Liver Disease Network (between the years 1999 and 2001) found that 91% of persons in the cohort had liver injury related to one of the diseases listed in Table 1.1 [1]. In a smaller cohort examined at a single center in the United Kingdom, the most common diagnoses that prompted an outpatient hepatology referral were nonalcoholic fatty liver disease (NAFLD, 29.5%), chronic hepatitis C (17.5%), alcoholic liver disease (17.5%), unspecified hepatitis (7.5%), and drug-induced liver injury (DILI, 4%). Other causes, such as Wilson disease, α_1-antitrypsin deficiency, and congestive hepatopathy, each accounted for <1% of new patient visits [2].

Many patients with acute or chronic liver injury are asymptomatic, and when symptoms do occur, they are often nonspecific. Presenting symptoms may include abdominal discomfort, anorexia, nausea, vomiting, fatigue, malaise, fever, rash, pruritus, or jaundice. Careful questioning about risk factors for certain conditions can provide insight into the likely nature of the liver injury.

Toxins, including alcohol and prescribed medications, are common causes of abnormal liver biochemical test levels and chronic liver disease. DILI may occur from either prescription or over-the-counter medications, including dietary and herbal supplements, and a careful medication history including prescription and nonprescription medications, supplements, and herbal remedies should be obtained. DILI can present with either acute or chronic liver injury and can range in severity from mild hepatitis or cholestasis to acute liver failure. The estimated incidence of DILI is 19.1 cases per 100 000 population, and DILI accounts for 10% of all cases of acute liver failure [3]. The most common classes of drugs implicated in DILI are antimicrobial agents (most notably amoxicillin-clavulanic acid, isoniazid, and nitrofurantoin) and dietary and herbal supplements [4], but any class of drug may be responsible.

In alcoholic liver disease, gender and the quantity of alcohol use are the primary predictors of hepatic injury and fibrosis. Gender is an important risk factor for clinically significant alcoholic liver disease, with women developing liver injury at lower levels of daily alcohol consumption than men. The daily threshold of alcohol intake for the development of cirrhosis is 40–60 g of alcohol in men, but only 20 g in women. With one alcoholic drink defined as containing 14 g of ethanol (the amount contained in 5 ounces (150 mL) of wine, 12 ounces (360 mL) of beer, or 1.5 ounces (45 mL) of 40-proof alcohol), the risk of alcoholic liver disease in women is associated with more than one drink daily, compared with at least two drinks daily for men [5]. The amount and type of alcohol consumed, along with the duration of alcohol use, should be carefully assessed to determine a patient's risk for alcoholic liver disease. Patients frequently underreport the quantity of consumption, and obtaining additional history from family members or close social contacts is often helpful. The CAGE (attempts to *c*ut back, *a*nnoyed about drinking, *g*uilt regarding drinking habits, use of *e*ye opener) criteria have long been used as a marker of alcohol misuse. An increasingly utilized screening test for alcohol dependence is the Alcohol Use Disorders Identification Test (AUDIT-C), which has been shown to predict the risk of alcohol-related gastrointestinal illness, including liver disease [6]. AUDIT-C utilizes three questions and has been validated for identifying persons with alcohol abuse or dependence [7] (Box 1.1).

Table 1.1 Clinical features of the most common causes of liver injury and chronic liver disease in a cohort of 1040 patients in the Chronic Liver Disease Network.

Cause of elevated liver biochemical test levels	Features from patient's history	Pertinent physical examination findings
Hepatitis C	Injection drug or intranasal cocaine use Blood transfusions prior to 1992 Needlestick exposure Birth between 1945 and 1965	Scarring from injection drug use Purpura Porphyria cutanea tarda
Alcohol-related liver disease	Quantification of daily alcohol intake Duration of alcohol use Positive AUDIT-C questionnaire (see Box 1.1)	Dupuytren's contractures
Nonalcoholic fatty liver disease	Age >40 years old Metabolic syndrome Diabetes mellitus	BMI >29.9 Increased waist-hip ratio
Hepatitis B	Injection drug use High-risk sexual activity Country of birth	—
Primary biliary cholangitis	Female gender Fatigue Pruritus History of osteoporosis History of autoimmune disease	Xanthelasma and xanthomas Skin excoriations Melanosis
Hereditary hemochromatosis	Family history of cirrhosis Diabetes mellitus Arthralgias	Skin hyperpigmentation
Primary sclerosing cholangitis	Bloody diarrhea History of inflammatory bowel disease Pruritus	Erythema nodosum
Autoimmune hepatitis	Arthralgias History of autoimmune disease	—
Drug-induced liver disease	Use of prescription drugs, herbal or dietary supplements, or over-the-counter medications	—
Celiac disease	Altered bowel habits Iron deficiency Rash	Dermatitis herpetiformis

AUDIT-C, Alcohol Use Disorders Identification Test; BMI, body mass index.
Data from [1].

Risk factors for viral hepatitis should also be identified. The most common risk factors for hepatitis C virus (HCV) infection in the United States are injection drug use, blood transfusions prior to 1992 [8], and needlestick occupational exposures. Additional risk factors have also been recognized, including the sharing of snorting straws [9] and high-risk sexual behaviors, such as anal receptive intercourse [10]. All persons born in the United States between the years 1945 and 1965 are at increased risk of chronic hepatitis C relative to the remaining population, with an estimated prevalence of 3.25%, prompting the Centers for Disease Control and Prevention to recommend screening for HCV infection for all persons in this birth cohort [11]. Coexisting hereditary hemochromatosis (HH) accelerates liver fibrosis due to HCV infection or alcohol but infrequently causes advanced fibrosis in the absence of a cofactor [12]. A strong family history of liver disease or cirrhosis raises suspicion for HH, and a personal history of arthralgias, skin discoloration, or diabetes mellitus is suggestive of underlying HH in the appropriate clinical setting.

Although hepatitis B is a vaccine-preventable disease, only 32.2% of US-born persons aged 19–49 have received ≥3 doses of the hepatitis B virus (HBV) vaccine. Injection drug use and high-risk sexual behaviors remain important risk factors for HBV infection in the United States, and the

Box 1.1 AUDIT-C questionnaire.

1 How often do you have a drink containing alcohol?
   - **a** Never
   - **b** Monthly or less
   - **c** 2–4 times per month
   - **d** 2–3 times per week
   - **e** 4 or more times a week

2 How many standard drinks containing alcohol do you have on a typical day?
   - **a** 1 or 2
   - **b** 3 or 4
   - **c** 5 or 6
   - **d** 7 to 9
   - **e** 10 or more

3 How often do you have six or more drinks on one occasion
   - **a** Never
   - **b** Less than monthly
   - **c** Monthly
   - **d** Weekly
   - **e** Daily or almost daily

Points are assigned for each answer: a – 1, b – 2, c – 3, d – 4, e – 5. A score of ≥4 is identifies persons with alcohol abuse with sensitivity of 0.79 and specificity of 0.56 in men.

Box 1.2 The National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome.

Three of the following five clinical characteristics must be present:

1 Abdominal obesity (waist circumference >101 cm (40 inches) in men, >89 cm (35 inches) in women)
2 Serum triglycerides >150 mg/dL
3 Serum high-density lipoprotein level <40 mg/dL in men or <50 mg/dL in women
4 Blood pressure ≥130/85 mmHg
5 Fasting plasma glucose ≥100 mg/dL

incidence of HBV infection is high in areas where injection drug use is common [13]. Foreign-born persons are also at higher risk of harboring HBV infection, with the highest rates, up to 33%, in persons of Asian descent [14]. Therefore, high-risk sexual behaviors, injection drug use, and country of origin are all important elements of a patient's history for assessing the risk of chronic HBV infection.

NAFLD has emerged as the most prevalent chronic liver condition in the United States, with estimated prevalence rates of 30–46% of adults [15] and 70% of obese or diabetic persons [16]. The clinical burden of NAFLD in the United States is staggering, and it is therefore critical to attempt to distinguish persons who have nonalcoholic steatohepatitis (NASH), and who are thus at risk for progressive inflammation, fibrosis, and cirrhosis, from those with simple steatosis (fatty liver) alone. Important risk factors for NASH include age >40 years, body mass index (BMI) ≥30, metabolic syndrome (Box 1.2), type 2 diabetes mellitus, and persistently elevated serum aminotransferase levels [17].

After drugs and toxins, viral hepatitis, and NAFLD, autoimmune and autoinflammatory liver diseases comprise most of the remaining causes of chronic liver injury. In middle-aged women with an elevated alkaline phosphatase level, primary biliary cholangitis (PBC, formerly primary biliary cirrhosis) is a principal consideration. PBC is much more common in women than men and is associated with other autoimmune diseases, in particular Raynaud's disease and Sjögren's syndrome. When symptomatic, persons with PBC commonly present with fatigue (estimated frequency of 20–85%) and pruritus (20–75%). Other clinical features include jaundice (10–60%), osteoporosis (35%), and an elevated serum cholesterol level (>75%), with a correlation between the degree of cholesterol elevation and the severity of cholestasis [18,19]. From 5% to 10% of persons with PBC may have negative testing for antimitochondrial antibodies, thereby increasing the importance of clinical assessment.

Autoimmune hepatitis, like PBC, is seen more commonly in women than men and in persons with concomitant autoimmune diseases. A wide spectrum of autoimmune diseases has been associated with autoimmune hepatitis, most commonly autoimmune thyroiditis and type 1 diabetes mellitus [20]. The clinical presentation of autoimmune hepatitis varies from asymptomatic disease to fulminant hepatitis in 25% of cases. In patients with symptomatic disease, joint symptoms and fatigue are common [21].

Luminal gastrointestinal diseases may manifest with liver biochemical test abnormalities and evidence of chronic liver injury. For example, up to 40% of patients with untreated celiac disease have elevated serum aminotransferase levels [22]. A history of altered bowel habits, iron deficiency, weight loss, rash, or osteoporosis should raise suspicion for underlying celiac disease. A history of bloody diarrhea, rash, or known history of inflammatory bowel disease suggests the possibility of primary sclerosing cholangitis.

Other less common liver diseases may also be suggested by careful questioning. For example, a history of pulmonary symptoms suggests α_1-antitrypsin deficiency or sarcoidosis. In a young patient with a comorbid neurologic or psychiatric disturbance, Wilson disease should be considered. The neurologic features of Wilson disease relate in part to basal ganglia dysfunction and include akinetic rigid syndrome similar to parkinsonism, psuedosclerosis with tremor, ataxia, and dystonia. Dysarthria, dysphagia, incoordination, and spasticity are typical. Migraines, insomnia, seizures, and depression

may occur. Recurrent unexplained fever suggests granulomatous hepatitis in a patient with a cholestatic pattern of liver biochemical test results.

Physical examination

The physical examination in the patient with abnormal liver biochemical test results or known liver disease seeks not only to provide clinical clues to the etiology of underlying liver injury, but also to determine whether there may be underlying advanced fibrosis or cirrhosis. Indeed, up to one third of patients who present for an outpatient hepatology consultation already have underlying cirrhosis [2].

Vital signs provide initial important data, particularly in identifying risk factors for NAFLD, which is suggested by an elevated BMI, increased waist circumference, and hypertension. Conversely, hypotension or a widened pulse pressure is often seen in the vasodilatory state associated with advanced cirrhosis.

Inspection of the patient begins with a determination whether the patient appears older than his or her stated age, the muscles are atrophied (e.g., temporal wasting), suggesting the catabolic state of cirrhosis, the parotid glands are enlarged, as is typical of alcoholic cirrhosis, and frank jaundice is present. Jaundice is assessed most readily by inspection of the eyes: in patients with scleral icterus (or, more accurately, conjunctival icterus), the whites of the eyes appear yellowed due to deposition of bilirubin in the conjunctivae, generally when serum bilirubin levels exceed 2.5 mg/dL [23]. Kayser–Fleischer rings, caused by deposition of copper in Descemet's membranes of the cornea, and "sunflower" cataracts may occasionally be seen in patients with Wilson disease but often require slit-lamp examination for detection. Persons who abuse alcohol or drugs may have poor dentition.

Skin

Liver diseases have a myriad of cutaneous manifestations, and after the general inspection of the patient, a careful skin examination may yield important insights (Fig. 1.1). The examiner may begin with the patient's hands and nails. Palmar erythema is a result of increased circulating estradiol levels and raises suspicion for cirrhosis. A number of nailbed findings may be found in patients with liver disease. Terry's nails are characterized by a proximal white discoloration of the nail and are associated with cirrhosis. Terry's nails and palmar erythema are not sensitive for cirrhosis but are quite specific (with specificities of 97% and 91%, respectively) [24,25]. Blue lunules, due to copper deposition, may be seen in Wilson disease. Clubbing of the fingernails and central cyanosis, most commonly associated with pulmonary disease, may be found in patients with cirrhosis, especially those with hepatopulmonary syndrome [24]. Dupuytren's contractures, characterized by fibrosis of the palmar fascia that pulls one or more fingers into flexion, is associated with alcohol use, although it does not correlate with the severity of liver

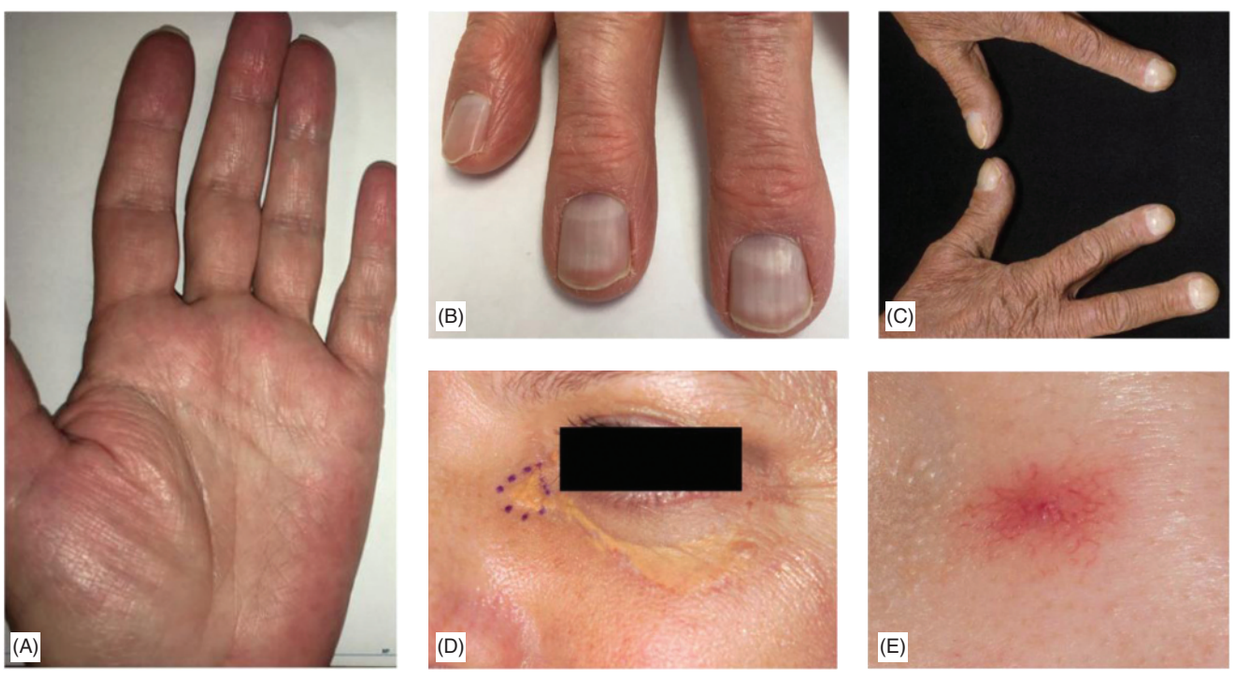

Figure 1.1 Cutaneous findings in cirrhosis. (A) Palmar erythema. (B) Terry's nails. (C) Clubbing. (D) Xanthelasma. (E) Spider telangiectasia. (C–E: Reproduced from [24] with permission from John Wiley & Sons.)

disease in alcoholics [26]. Spider telangiectasias are cutaneous vascular lesions characterized by "spidery" vessels that radiate from a central arteriole and that may be seen with acute or chronic liver disease. When pressure is applied to the lesion it blanches and then fills from the central arteriole outward. Spider telangiectasias are found in the distribution of the superior vena cava and are more often anterior than posterior on the body. Additionally, they have been associated with clinically significant portal hypertension in the setting of established cirrhosis [27].

Specific causes of chronic liver disease may have characteristic cutaneous manifestations. PBC, in particular, has associated dermatologic manifestations, and, in one series [28], nearly 40% of patients with PBC presented with a dermatologic complaint. Typical findings include xanthelasma and xanthomas, which are yellowish deposits near the inner canthus of the eyelids and on the palms of the hands, respectively. They reflect the dyslipidemia associated with PBC, and although uncommon, they are quite specific for advanced PBC among patients with liver disease. Hyperpigmentation, excoriations, and skin lichenification due to pruritus and scratching are also common skin findings in patients with PBC and other chronic cholestatic disorders [24]. Other less common skin findings related to liver disease include a slate gray or bronze coloration of the skin in HH, nonpalpable purpura due to HCV-related mixed cryoglobulinemia, a vesicular rash on the dorsum of the hands in porphyria cutanea tarda due to HCV infection and iron overload, and dermatitis herpetiformis related to underlying celiac disease.

Abdomen

Situated in the right upper quadrant, the liver may infrequently extend 5–6 cm across the midline to the left upper quadrant. The upper convex surface is tucked under the diaphragm at the level of the fifth or sixth anterior rib. The lower surface is concave, with the gallbladder tucked in it, and generally not palpable in healthy persons. The liver edge runs parallel with the right costal margin. Respiration drives the liver downward with an excursion of 2–3 cm. There is great variability in the shape of the liver [29].

Although abdominal imaging is often relied on to support the abdominal examination findings in the clinical evaluation of liver disease, a number of important findings are best determined by simple inspection, auscultation, and palpation. Abdominal, and specifically hepatic, tenderness can only be elicited by direct examination. Inspection of the abdomen may reveal signs of decompensated liver disease (see later), such as distention, bulging flanks, or distended abdominal veins on the anterior abdominal wall. To facilitate the abdominal examination, the patient should remain supine with the legs flexed at the knee to relax the anterior abdominal musculature.

Auscultation of the abdomen classically has involved placing the stethoscope over all four quadrants to assess bowel sound activity and additionally in the flanks and back to detect bruits. The reliability of auscultation to determine clinical pathology from bowel sounds, however, has come into question, with one study finding low sensitivity and poor inter-rater reliability [30]. Nevertheless, a number of auscultatory findings have been described in the setting of liver disease. Portosystemic shunting may be associated with a low-pitched continuous venous hum, and a continuous hum at the umbilicus, known as the Cruveilhier–Baumgarten bruit, is thought to be due to shunting in the abdominal wall due to a patent umbilical vein [31]. Auscultation has also been utilized to determine the liver span by the scratch test (see later). Rare auscultatory findings include a harsh systolic bruit over the liver in patients with hepatocellular carcinoma or alcoholic hepatitis and a peritoneal friction rub (like two pieces of leather rubbing together) in patients with perihepatitis or hepatocellular carcinoma or after a liver biopsy. A rub over the spleen may be heard after a splenic infarct. Rarely, continuous murmurs are heard with a hepatic hemangioma or an arteriovenous fistula in the splanchnic circulation.

An estimation of liver span is an important element of the clinical examination of the patient with liver disease [29]. The liver span may vary with a person's height and gender, and the liver size generally correlates with body size and liver shape correlates with body habitus. The average liver diameter in healthy persons has been estimated to be 7 cm in women and 10.5 cm in men [32]. In general, hepatomegaly is unlikely if the liver span by gentle percussion is less than 12 cm [29]. An enlarged liver may be seen in acute and chronic hepatitis, whereas the liver often shrinks as fibrosis progresses and cirrhosis advances. Marked enlargement of the liver may be seen in patients with primary or metastatic hepatic tumors (including lymphoma), alcoholic liver disease, severe heart failure (with a pulsatile liver in tricuspid regurgitation), and infiltrative liver diseases such as amyloidosis, myelofibrosis, and chronic myelogenous leukemia. Techniques employed to determine liver span include the scratch test and percussion. The underlying principle of the scratch test is that the solid liver will transmit sound with a greater intensity than the other, hollow, viscera of the abdominal cavity. The stethoscope is placed just below the xyphoid process. The clinician begins by gently stroking the skin of the lower right abdomen in the midclavicular line and advancing steadily upward until the sound heard through the stethoscope abruptly increases in volume – the point thought to represent the lower edge

of the liver. This finding is quite reliable between examiners but may not reliably demonstrate the true location of the liver edge when compared with ultrasonography [33].

Percussion of the abdomen is commonly utilized to determine the liver span and can also be used to assess splenomegaly. To map the size of the liver, both the upper and lower borders should be percussed lightly in the midclavicular line. After the liver span is assessed in the midclavicular line, percussion may be extended into the epigastrium. In the midclavicular line, the upper border is near the right nipple and the lower border lies just under the right costal margin. Dullness to percussion that is present in the epigastrium raises concern for left hepatic lobe hypertrophy, which is often seen in cirrhosis [34]. With left hepatic lobe hypertrophy from cirrhosis, the liver span in the midsternal line will be similar to, or greater than, the liver span in the midclavicular line (Fig. 1.2).

Splenomegaly also raises concern for cirrhosis and portal hypertension and is generally assessed by palpation, but percussion may also be performed. Two percussion techniques have been used: percussion in the space of Traube and elicitation of Castell's sign. The space of Traube is defined as the sixth rib superiorly, the left midaxillary line laterally, and the left costal margin inferiorly. With the patient supine, this area is expected to be resonant, or tympanitic; dullness suggests splenomegaly. Compared with ultrasonography, this maneuver has a sensitivity and specificity of 62% and 72%, respectively. To elicit Castell's sign, the left anterior axillary line is percussed at the lowest intercostal space. The area is normally resonant. Splenomegaly is diagnosed if the percussion note becomes dull with deep inspiration, when the enlarged spleen descends. Castell's sign has a sensitivity and specificity of 82% and 83%, respectively [35].

Palpation can often detect splenomegaly and determine the contour and tenderness of the liver edge, but the detection of the liver by palpation does not correlate closely with liver size by imaging, and in some cases a nonpalpable liver may still be enlarged [29]. When splenomegaly is present, the enlarged spleen can be felt by pressing gently with the right hand just below the left costal margin in the anterior axillary line, while the examiner's left hand is placed in the left flank for counterpressure. The patient is asked to inspire deeply, and the spleen tip is sought between the subcostal margin and the umbilicus. If the spleen edge is not detected, the examination may be repeated with the patient in the right lateral decubitus position with the knees flexed. Conversely, in the setting of massive splenomegaly, the spleen edge may be missed if palpation does not begin in the lower abdomen above the iliac crest. Detection of splenomegaly by palpation implies that the spleen size is at least two- to three-fold above normal.

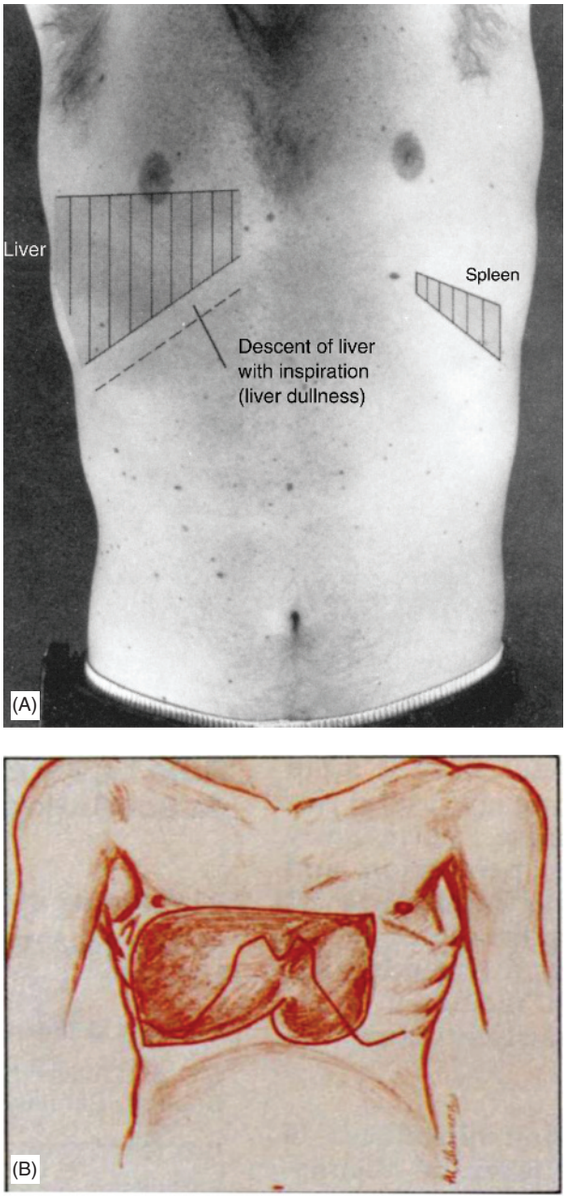

Figure 1.2 Percussion of the liver in cirrhosis. (A) Image of the abdomen and chest showing location of the liver and spleen. In healthy persons, the liver descends 1–3 cm with deep inspiration. (B) In cirrhosis, there may be shrinking of the right lobe of the liver with enlargement of the left and caudate lobes. This results in the finding of an enlarged liver span in the midsternal line and palpation of the liver edge in the epigastrium. (Reproduced from [34] with permission from Taylor and Francis, www.tandfonline.com.)

To palpate the liver edge, the examiner begins palpation in the right lower quadrant and proceeds gently upward to the expected lower edge of the liver at the right costal margin. A normal liver may rest entirely below the rib cage; to assist with palpation of the liver the examiner's

Table 1.2 Findings on percussion and palpation of the liver in various conditions.

Condition	Liver size	Contour and firmness	Tenderness
Acute hepatitis	Enlarged	Smooth	May be quite tender
Chronic hepatitis	May be enlarged	Firm	May or may not be tender
Cirrhosis	Small, relatively large left lobe	Firm, may be nodular	Nontender
Right heart failure	Enlarged	Firm	Tender
Neoplasms of the liver	Enlarged	Hard, nodular	Nontender

left hand may be placed posteriorly beneath the patient below the twelfth rib to lift the liver gently upward, and the patient may be asked to take a deep breath as the liver edge descends inferiorly with deep inspiration. In healthy persons, the liver edge may be felt when the patient takes a slow, deep inspiration with relaxed abdominal muscles. In obese persons, the "hooking" technique may be helpful. With the examiner to the right of the patient's chest, both hands are placed, side by side, on the right upper quadrant below the border of liver dullness with the fingers curled around the costal margin. The liver edge is felt when the patient takes a deep breath. Riedel's lobe is an anatomic variant of the liver in which the right lobe extends in a tongue-like projection into the right lower quadrant and can be palpated in a healthy person. As noted earlier, palpation of the liver in the epigastrium is suggestive of advanced hepatic fibrosis. The size, contour, firmness and presence or absence of tenderness of the liver provide insight into the underlying disease (Table 1.2). With pressure in the right upper quadrant, the examiner may also assess the patient for hepatojugular reflux suggestive of congestive hepatopathy (and exclusion of hepatic vein thrombosis). A pulsatile liver is characteristic of tricuspid regurgitation and may be seen in constrictive pericarditis.

Although laboratory testing, imaging, and in some cases liver biopsy are required to confirm a diagnosis of cirrhosis, physical examination findings may heighten clinical suspicion and identify patients for whom a liver biopsy may be warranted to diagnose cirrhosis. Several physical examination findings in patients with cirrhosis are thought to be related to impaired intrahepatic metabolism of androstenedione, with a resulting increase in the peripheral conversion of andostenedione to estradiol and estrogen. These findings include palmar erythema, spider telangiectasias, gynecomastia and testicular atrophy in men, and diminished body hair. The consequence of severe hepatocellular dysfunction and portal hypertension are often more readily apparent and include ascites, caput medusae, an umbilical hernia, asterixis, and frank jaundice (see later). The sensitivity and specificity of physical findings for the clinical detection of cirrhosis are summarized in Table 1.3. Most findings are quite specific for cirrhosis but have poor sensitivity. The presence of spider telangiectases, palmar erythema, and a firm liver edge on palpation are among the most sensitive findings.

Table 1.3 Sensitivity and specificity of various physical examination findings for the detection of cirrhosis.

Finding	Sensitivity	Specificity
Firm liver edge	0.73	0.81
Spider telangiectasias	0.46	0.89
Palmar erythema	0.46	0.91
Terry's nails	0.43–0.44	0.97–0.98
Decreased body hair	0.36	0.97
Splenomegaly	0.34	0.90
Jaundice	0.28	0.93
Gynecomastia	0.18–0.58	0.97–0.98

Data from [25].

Jaundice

The patient with frank jaundice requires a different diagnostic formulation and clinical approach from that for the patient with asymptomatic elevations of the serum liver enzyme levels. Categories of diagnostic possibilities include extrahepatic biliary obstruction, intrahepatic biliary disease, and hemolysis or other causes of indirect (unconjugated) hyperbilirubinemia. Whether jaundice is due to conjugated or unconjugated hyperbilirubinemia can be hinted at clinically by eliciting a history of darkening of the urine, because unconjugated bilirubin cannot be excreted by the renal tubules and does not result in dark urine. In the past, it was observed that hemolytic jaundice has a light yellow color on eye examination, whereas hepatic jaundice is orange-yellow; however, the distinction is best assessed with biochemical testing. When jaundice is due to direct hyperbilirubinemia, the evaluation focuses on extrahepatic biliary obstruction, severe hepatocellular injury, and intrahepatic cholestasis, including rare disorders of bilirubin metabolism such as Dubin–Johnson or Rotor syndrome (Table 1.4). Fulminant Wilson disease is rare but should be considered in young

Table 1.4 Differential diagnosis of direct hyperbilirubinemia.

Cause of jaundice	Historical elements	Physical examination findings
Extrahepatic biliary obstruction		
Choledocholithiasis	Epigastric or RUQ abdominal pain	Fever
Ascending cholangitis	Fever, chills	Palpable, tender gallbladder
Benign biliary stricture	Acholic stools	Abdominal tenderness
Malignant obstruction	Weight loss	Cachexia
Pancreatic cancer	Malaise, fatigue	Courvoisier's sign (see text)
	Anorexia	Hepatomegaly
	Pruritus	Ascites
	Diabetes mellitus	
	Smoking	
	Prior pancreatitis	
Severe hepatocellular injury		
Acute viral hepatitis	Anorexia, malaise	Fever
Autoimmune hepatitis	Rash	Tender hepatomegaly
	Fever	Reticular rash
	Arthralgias	
Acute alcoholic hepatitis	History of heavy alcohol use	Fever
	Recent binge drinking	Tender hepatomegaly
		Ascites
Drug-induced liver injury	New medication use	Hepatomegaly
	Supplement use	Excoriations (if pruritus)
Ischemic hepatitis	Critical Illness, hypotension	Critically ill patient
Decompensated cirrhosis	Prior history of liver disease	Muscle wasting
	Increasing abdominal girth	Ascites
	Pedal edema	Asterixis
	Altered mental status	
Intrahepatic cholestasis		
Primary biliary cholangitis	Pruritus, fatigue, history of IBD	Excoriations, xanthoma, xanthelasma, erythema nodosum
Primary sclerosing cholangitis		
Familial or benign intrahepatic cholestasis	Pruritis, jaundice	—
Infiltrative diseases	Weight loss	Hepatomegaly
Metastatic malignancy	Fatigue	Palpable abdominal masses
Sepsis	Critical illness	Critically ill patient
	TPN Mechanical ventilation	
Inherited disorders of bilirubin metabolism		
Dubin–Johnson syndrome	Mild, chronic icterus Pruritus	Jaundice
Rotor syndrome		
Other bile transport disorders		

IBD, inflammatory bowel disease; RUQ, right upper quadrant; TPN, total parenteral nutrition.

persons, particularly females, with jaundice and acute hepatic dysfunction.

For the patient presenting with the insidious onset of clinically evident jaundice, the clinician must harbor particular suspicion for malignant biliary obstruction. In one series of patients presenting with jaundice, the most common cause was malignancy, followed by sepsis, alcoholic liver disease, cirrhosis, and gallstone disease [36]. A history of anorexia, weight loss, and vague abdominal discomfort may suggest a malignant cause. Pancreatic cancer is strongly associated with smoking and diabetes mellitus, and an attack of pancreatitis may pre-date the diagnosis of pancreatic cancer [37]. On physical examination, wasting and cachexia may be evident. In addition to jaundice, skin examination may reveal excoriations due to pruritus. A suggestive physical examination finding in patients with pancreatic or ampullary cancer is Courvoisier's sign – painless and palpable distention of the gallbladder that is thought to result from gradually progressive bile duct obstruction. To detect the enlarged gallbladder, the examiner palpates the angle formed between the lateral edge of the rectus abdominus muscle and the right costal margin. Courvoisier's sign, however, is present only in approximately 13% of patients presenting with jaundice due to

pancreatic cancer; hepatomegaly and jaundice are more common physical examination findings [38]. Nor is Courvoisier's sign specific for a malignant cause of biliary obstruction. A firm umbilical mass ("Sister Mary Joseph's node") indicates intra-abdominal malignancy.

Gallbladder disease and choledocholithiasis are common causes of jaundice due to extrahepatic biliary obstruction. Biliary obstruction due to choledocholithiasis may be complicated by acute cholangitis, which is characterized clinically by the triad of fever, abdominal pain, and jaundice (Charcot's triad), in severe cases complicated by hypotension and altered mental status (Reynolds' pentad). On examination, the right upper quadrant is typically tender, and on occasion the gallbladder may be palpable.

The clinical evaluation of patients with intrahepatic causes of jaundice parallels the evaluation of abnormal liver biochemical test levels discussed earlier. A carefully taken history of medication and supplement use is required to exclude DILI. The severity of icteric DILI may range from asymptomatic jaundice to acute liver failure. Acute viral hepatitis presents with jaundice when there is severe hepatocellular injury. Etiologic agents include hepatitis A, B, C, D, and E viruses, as well as Epstein–Barr virus, herpes simplex virus, and cytomegalovirus. When acute hepatitis C presents clinically with jaundice, immune clearance of the virus is substantially more likely than when hepatitis C presents without jaundice [39]. Symptoms of acute viral hepatitis may include anorexia, malaise, fever, rash, and abdominal pain. In addition to assessing for risk factors for hepatitis B and C, a history of recent travel, unusual food exposures, and sick contacts should be elicited. The clinical presentation of autoimmune hepatitis may be similar to that of acute viral hepatitis but with negative serologic testing for a viral etiology.

Alcoholic hepatitis is an acute and potentially severe form of alcoholic liver disease and may occur with or without underlying advanced fibrosis. Like alcohol-related cirrhosis, alcoholic hepatitis is associated with excessive alcohol use over a prolonged period of time. A history of a recent increase in alcohol intake or binge drinking and the type of alcohol imbibed (beer and spirits more than wine) are also risk factors for acute alcoholic hepatitis [40]. In addition to jaundice, symptoms may include fever, new-onset ascites, and abdominal pain. On physical examination, the patient may or may not have cutaneous stigmata of liver disease but will commonly have tender hepatomegaly; ascites and evidence of hepatic encephalopathy may be present. Skin findings may include palmar erythema, facial and upper body telangiectasias, and palmar Dupuytren's contractures. Jaundice also may signal decompensation of established cirrhosis, which merits additional evaluation as discussed later.

Known or suspected compensated or decompensated cirrhosis

The objective of the clinical evaluation of a patient with known cirrhosis or decompensated liver disease is not only to determine likely causes of liver injury and confirm evidence of advanced hepatic fibrosis, but also to assess the patient for complications of cirrhosis (Table 1.5). The natural progression of cirrhosis has been considered to be one of a period of stability with few complications followed by decompensation heralded by the onset of ascites, variceal hemorrhage, or encephalopathy, with an estimated mean 2-year survival following initial decompensation. The prognosis of a patient with cirrhosis may be further stratified by the type and number of complications. In patients with varices without bleeding, the 5-year mortality rate is relatively low at 10%; however, with additional complications of portal hypertension, the mortality rate increases to 30%, and with more than one complication, the 5-year mortality rate approaches 90% [41]. The concept of acute-on-chronic liver failure (ACLF) has been introduced to describe the abrupt onset of multiorgan dysfunction in the setting of chronic liver injury, compensated cirrhosis, or decompensated cirrhosis [42]. When decompensated cirrhosis is further complicated by infectious complications or acute kidney injury, the 1-year mortality rate has been estimated to be 67% [43].

Patients with compensated cirrhosis may have few or no symptoms related to liver disease or symptoms specific to the underlying cause of cirrhosis. When present, symptoms may include fatigue, muscle wasting, easy bruising or bleeding, and subtle cognitive changes. With decompensation, patients often present to medical attention with overt clinical symptoms pointing to the nature of the complicating event (e.g., variceal hemorrhage, ascites).

History taking

The patient with cirrhosis may present for routine examination or with specific clinical complaints related to decompensation. In the asymptomatic patient, the focus of the history is mainly to ensure that appropriate preventive lifestyle measures are being followed. Abstinence from alcohol is recommended for all patients with cirrhosis, irrespective of etiology, and alcohol intake should be assessed at each visit. For patients with insulin resistance and obesity, which are independently linked to adverse outcomes in patients with cirrhosis, weight loss and glucose control should be encouraged and monitored.

In a patient with cirrhosis with a new complication or worsening of a known complication, additional history taking should focus on the driving etiology and clinical severity of the complication. Ascites may present with the new onset of pedal or leg edema or increasing abdominal

Table 1.5 Complications of decompensated liver disease.

Complication	Historical elements	Physical examination findings
Ascites/edema	Weight gain	Bulging flanks
	Ankle swelling	Flank dullness
	Increased abdominal girth	Shifting dullness
		Fluid wave
Encephalopathy	Sleep–wake cycle reversal	Asterixis
	Personality changes	Mental status assessment
	Inattentiveness	Abnormal PHES
	Confusion	
Gastrointestinal bleeding: varices, portal hypertensive gastropathy	Weakness, lightheadedness	Fecal occult blood or melena
	Melena	
	Hematemesis	
Jaundice	New medication use	Scleral icterus
	Diminished urine output	Jaundice
	Symptoms of infection	
	Weight loss	
	Alcohol use	
Decreased blood pressure, renal injury	Decreased urine output	Systolic blood pressure <100 mmHg
	Dark urine	MAP <82 mmHg
	Lightheadedness	Orthostatic hypotension
Coagulopathy	Epistaxis	Ecchymoses
	Gum bleeding	
	Easy bruising	
Spontaneous bacterial peritonitis	Fevers, chills	Fever
	Abdominal pain	Abdominal tenderness
	Diminished urine output	Encephalopathy
	Evidence of gastrointestinal bleeding	

MAP, mean arterial pressure; PHES, Psychometric Hepatic Encephalopathy Score.

girth. In a patient with the new onset of ascites, potential contributors include excessive or recurrent alcohol use, poor glucose control, increased sodium intake, heart or renal failure, or interval development of portal vein thrombosis. In a patient already on diuretic therapy, recurrent ascites suggests medication nonadherence, poor dietary sodium restriction, or progressive decompensation. Spontaneous bacterial peritonitis is a feared complication of decompensated cirrhosis, with clinical suspicion raised by abdominal pain and fever, although deterioration in liver function may be the only manifestation.

In a patient with new overt hepatic encephalopathy, careful assessment for potential precipitants is required, including use of new or sedating medications, infections, gastrointestinal bleeding, electrolyte imbalance (particularly hypokalemia), dehydration, or new renal impairment. The clinician should review all drugs, including over-the-counter medications, taken by the patient and ask about a recent history of fever, abdominal pain, melena, hematochezia, pedal edema, increasing abdominal girth, and diminished urine output.

The new onset of jaundice in a previously well-compensated patient with cirrhosis is a cause for concern because it may signal the development of ACLF. Careful questioning regarding any possible triggers, such as new medications or supplements, alcohol use, evidence of infection, abdominal pain, decreased urine output, or increased abdominal girth, should heighten clinical concern.

Physical examination

Careful assessment for objective evidence of complications of cirrhosis should be undertaken to guide management. For patients already receiving medical care for liver disease, the physical examination may also detect evidence of adverse events resulting from the medical management of liver disease.

Determination of the vital signs is of great value. Given the mortality associated with infectious complications of liver disease, fever in a patient with cirrhosis merits urgent evaluation, particularly if ascitic fluid is evident on clinical examination. The patient's blood pressure, including orthostatic vital signs, should be assessed; cirrhosis itself results in a vasodilatory state that may cause relative hypotension and that can be potentiated by medications such as nonselective beta receptor antagonists used

to prevent variceal bleeding. Nonselective beta receptor antagonists may increase mortality in patients with decompensated cirrhosis [44], and it has been suggested that beta receptor antagonists be discontinued when systolic blood pressure falls below 90 mmHg or mean arterial pressure falls below 82 mmHg, the serum sodium is less than 130 mEq/L, or acute kidney injury has developed [45].

Careful monitoring of weight is also important in the assessment of the patient with cirrhosis. Rapid weight gain raises concern for volume retention and the development of ascites, whereas weight loss in a patient with cirrhosis without ascites raises concern for malnutrition or the development of malignancy. For the patient with ascites, regular monitoring of weight is required to assess the adequacy of the diuretic regimen and of dietary sodium restriction.

The clinician should assess the patient with cirrhosis for scleral icterus or frank jaundice. Although there are limited objective measures, subjective assessment should be made of muscle mass or diminishing strength. The parotid glands may be enlarged (as may the lacrimal glands) especially in patients with alcoholic cirrhosis. The pungent odor of fetor hepaticus, caused by the portosystemic shunting of sulfur-containing thiols, may be detected when the patient exhales. A skin examination may reveal ecchymoses due to coagulopathy or an increasing number of spider telangiectasias suggestive of worsening portosystemic shunting.

Normally, the superficial veins of the abdominal wall are barely visible, but in a patient with cirrhosis, venous prominence may reflect inferior vena cava or portal vein obstruction. Pronounced dilatation of the periumbilical veins produces the pattern known as caput medusae. The direction of blood flow in the engorged veins may suggest the site of venous obstruction. Normal flow is away from the umbilicus, and portal hypertension does not alter the direction of flow. On the other hand, obstruction of the inferior vena cava causes upward flow from the lower abdomen, and obstruction of the superior vena cava causes downward flow from the upper abdomen. Blood flow can be assessed by compressing an abdominal wall vein with two fingers several centimeters apart and removing one finger to observe the rate of refilling; the maneuver is repeated with release of the other finger, and the direction of flow is thus determined.

A number of maneuvers may be utilized to detect ascites on physical examination. On inspection, bulging flanks may indicate the presence of ascites. Percussion of the abdomen in the supine position detects flank dullness if fluid is present laterally in the dependent areas. In obese patients, it may be challenging to detect bulging flanks and flank dullness, but shifting dullness may be detectable in these persons. To assess for shifting dullness, the most superior margin of abdominal dullness with the patient in the supine position is identified. The transition point between tympany and dullness represents the intra-abdominal air–fluid boundary. The patient is then asked to turn toward the examiner and assume a right lateral decubitus position, and the area of dullness is again percussed. If intra-abdominal free fluid is present, the area of dullness will shift toward the umbilicus. This maneuver should be performed with the patient on the left side as well to confirm the presence of ascites. Finally, the examiner may attempt to elicit a fluid wave (Fig. 1.3). The fluid wave requires either a second examiner or the participation of the patient, who places the ulnar surface of one or both hands firmly in the midline to hold subcutaneous adipose tissue in place. The examiner then taps one flank with one hand while the other hand is placed gently on the contralateral flank. Detection of an impulse by the examiner's second hand is considered to be a positive sign for the presence of fluid.

These physical examination maneuvers all have moderately good sensitivity but limited specificity, as detailed in Table 1.6 [46]. Diffuse abdominal tenderness in a patient with ascites raises clinical concern for spontaneous bacterial peritonitis.

The neurologic examination assumes additional importance in the evaluation of the patient with cirrhosis, because the development of overt hepatic encephalopathy portends decompensation and poor survival and

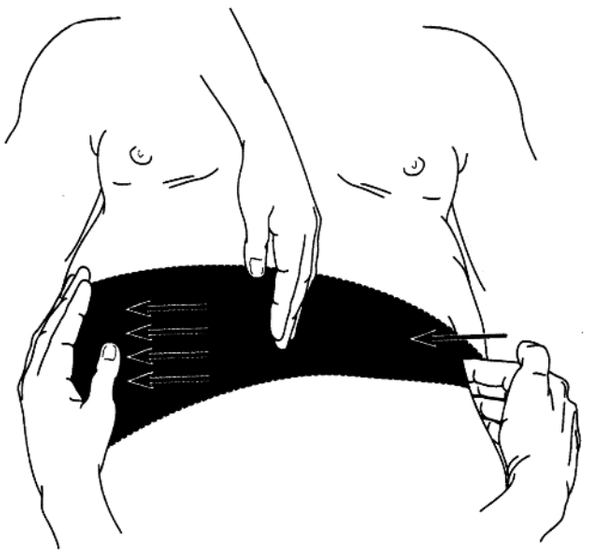

Figure 1.3 The fluid wave test for the detection of ascites. While an assistant (either a second clinician or the patient) places one hand firmly in the patient's abdominal midline, the examiner holds one hand still on the patient's right flank, while the other hand taps or presses firmly but gently on the left flank. Detection of an impulse in the right flank indicates the presence of fluid.

Table 1.6 Sensitivity and specificity of physical examination findings for the detection of ascites.

Finding	Sensitivity	Specificity
Flank dullness	0.84	0.59
Bulging flank	0.81	0.59
Shifting dullness	0.77	0.72
Fluid wave	0.62	0.9

Data from [46].

characteristic neurologic findings are seen in patients with Wilson disease. Hepatic encephalopathy has a broad spectrum of clinical manifestations from mild cognitive impairment to coma. Overt hepatic encephalopathy is often readily apparent in a patient who is agitated, confused, or somnolent. The West Haven criteria, developed in 1977 for the clinical assessment of encephalopathy, remain widely used in assessing the severity of overt hepatic encephalopathy (Table 1.7). On physical examination, asterixis is a characteristic finding in persons with clinically evident hepatic encephalopathy, although it is not specific for liver disease and can be seen with other toxic metabolic encephalopathies. Moreover, it cannot be elicited in comatose patients. The examiner asks the patient to hold one or both hands outstretched in dorsiflexion with eyes closed. Asterixis is the presence of a downward drift of the fingers followed by rapid correction, clinically recognized as a "flap." The patient with grade I or II encephalopathy may also have difficulty with simple tasks such as naming the days of the week backwards, subtracting 7 serially starting from 100, or drawing a square, spiral, or five-cornered star.

Identifying the patient with covert, or "minimal," hepatic encephalopathy is valuable, because the patient is at increased risk for falls, impaired driving ability, and daytime fatigue. The patient with covert hepatic encephalopathy may have an entirely normal clinical neurologic evaluation, but on more thorough neurocognitive testing, substantial deficits are identified. Despite the reassuring clinical examination, covert hepatic encephalopathy can have important impact on quality of life and activities of daily living. Formal neuropsychological testing is the most robust assessment for covert hepatic encephalopathy, although bedside pen-and-paper tests are often used in practice. The best-validated neuropsychological testing is the battery of tests that comprise the Psychometric Hepatic Encephalopathy Score (PHES), but the widespread clinical utility of the PHES has been limited due to its time-intensive nature and the lack of availability of the tools within the test itself [47]. One component of the PHES, the serial "dotting" test, has been translated into applications for a personal computer or mobile device (e.g., the Stroop test), potentially increasing the feasibility of its routine use in clinical practice. This test, administered alone, has a 68% sensitivity and 98.3% specificity for detecting covert or grade I hepatic encephalopathy [48]. The management of covert hepatic encephalopathy is an area of ongoing investigation; although increased vigilance for overt encephalopathy and patient counseling are recommended, the benefit of specific treatment for encephalopathy in this group of patient is not yet established [49].

Table 1.7 West Haven criteria: clinical assessment of the severity of hepatic encephalopathy.

Grade	Clinical features
I	Euphoria or depression, mild confusion, difficulty with computation tasks, sleep–wake cycle reversal; asterixis is variable
II	Moderate confusion, lethargy/apathy, agitation; asterixis is generally present
III	Somnolence, marked confusion and disorientation; asterixis may be absent
IV	Coma

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