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Jensen GL et al: GLIM criteria for the diagnosis of malnutrition: A con sensus report from the global clinical nutrition community. JPEN J Parenter Enteral Nutr 43:32, 2019. Singer P et al: ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. Clin Nutr 42:1671, 2023. Wischmeyer PE et al: Personalized nutrition therapy in critical care: 10 expert recommendations. Crit Care 27:261, 2023. Section 3 Liver and Biliary Tract Disease Marc G. Ghany, Jay H. Hoofnagle

Approach to the Patient

with Liver Disease A diagnosis of liver disease usually can be made accurately by careful elicitation of the patient's history, physical examination, and applica tion of a few laboratory tests. In some circumstances, radiologic exami nations are helpful or, indeed, diagnostic. Liver biopsy is considered the criterion standard in evaluation of liver disease but is now needed less for diagnosis than for grading (activity) and staging (fibrosis) of disease. Noninvasive means of assessing fibrosis stage have become increasingly helpful and may allow for avoidance of biopsy in an increasing proportion of patients. This chapter provides an introduc tion to diagnosis and management of liver disease, briefly reviewing the structure and function of the liver; the major clinical manifestations of liver disease; and the use of clinical history, physical examination, laboratory tests, imaging studies, and liver biopsy. LIVER STRUCTURE AND FUNCTION The liver is the largest organ of the body, weighing 1–1.5 kg and rep resenting 1.5–2.5% of the lean body mass. The size and shape of the liver vary and generally match the general body shape—long and lean or squat and square. This organ is located in the right upper quadrant of the abdomen under the right lower rib cage against the diaphragm and projects for a variable extent into the left upper quadrant. It is held in place by ligamentous attachments to the diaphragm, peritoneum, great vessels, and upper gastrointestinal organs. The liver receives a dual blood supply; ~20% of the blood flow is oxygen-rich blood from the hepatic artery, and 80% is nutrient-rich blood from the portal vein arising from the stomach, intestines, pancreas, and spleen. The majority of cells in the liver are hepatocytes, which constitute two-thirds of the organ's mass. The remaining cell types are Kupffer cells (members of the reticuloendothelial system), stellate (Ito or fatstoring) cells, endothelial and blood vessel cells, bile ductular cells, and cells of supporting structures. Viewed by light microscopy, the

liver appears to be organized in lobules, with portal areas at the periphery and central veins in the center of each lobule. However, from a func tional point of view, the liver is organized into acini, with both hepatic arterial and portal venous blood entering the acinus from the portal areas (zone 1) and then flowing through the sinusoids to the terminal hepatic veins (zone 3); the intervening hepatocytes constitute zone 2. The advantage of viewing the acinus as the physiologic unit of the liver is that this perspective helps to explain the morphologic patterns and zonality of many vascular and biliary diseases not explained by the lobular arrangement. Portal areas of the liver consist of small veins, arteries, bile ducts, and lymphatics organized in a loose stroma of supporting matrix and small amounts of collagen. Blood flowing into the portal areas is distributed through the sinusoids, passing from zone 1 to zone 3 of the acinus and

draining into the terminal hepatic veins (“central veins”). Secreted bile flows in the opposite direction—that is, in a countercurrent pattern from zone 3 to zone 1. The sinusoids are lined by unique endothelial cells that have prominent fenestrae of variable sizes, allowing the free flow of plasma but not of cellular elements. The plasma is thus in direct contact with hepatocytes in the subendothelial space of Disse.

Hepatocytes have distinct polarity. The basolateral side of the hepa tocyte lines the space of Disse and is richly lined with microvilli; it exhibits endocytotic and pinocytotic activity, with passive and active uptake of nutrients, proteins, and other molecules. The apical pole of the hepatocyte forms the canalicular membranes through which bile components are secreted. The canaliculi of hepatocytes form a fine network, which fuses into the bile ductular elements near the portal areas. Kupffer cells usually lie within the sinusoidal vascular space and represent the largest group of fixed macrophages in the body. The stel late cells are located in the space of Disse but are not usually prominent unless activated, whereupon they produce collagen and matrix. Red blood cells stay in the sinusoidal space as blood flows through the lob ules, but white blood cells can migrate through or around endothelial cells into the space of Disse and from there to portal areas, where they can return to the circulation through lymphatics. Hepatocytes perform numerous and vital roles in maintaining homeostasis and health. These functions include the synthesis of most essential serum proteins (albumin, carrier proteins, coagulation fac tors, many hormonal and growth factors), the production of bile and its carriers (bile acids, cholesterol, lecithin, phospholipids), the regulation of nutrients (glucose, glycogen, lipids, cholesterol, amino acids), and the metabolism and conjugation of lipophilic compounds (bilirubin, anions, cations, drugs) for excretion in the bile or urine. Measurement of these activities to assess liver function is complicated by the multi plicity and variability of these functions. Commonly used liver “function” tests are measurements of serum bilirubin, serum albumin, and pro thrombin time. The serum bilirubin level is a measure of hepatic con jugation and excretion; the serum albumin level and prothrombin time are measures of protein synthesis. Abnormalities of bilirubin, albumin, and prothrombin time are typical of hepatic dysfunction. Frank liver failure is incompatible with life, and the functions of the liver are too complex and diverse to be subserved by a mechanical pump; a dialysis membrane; or a concoction of infused hormones, proteins, and growth factors. CHAPTER 347 Approach to the Patient with Liver Disease LIVER DISEASES While there are many causes of liver disease (Table 347-1), these disor ders generally present clinically in a few distinct patterns and are usu ally classified as hepatocellular, cholestatic (obstructive), or mixed. In hepatocellular diseases (such as viral hepatitis and alcoholic liver dis ease), features of liver injury, inflammation, and necrosis predominate. In cholestatic diseases, such as gallstone or malignant obstruction,

primary biliary cholangitis (previously referred to as primary biliary cirrhosis), and some drug-induced liver diseases, features of inhibition of bile flow predominate. In a mixed pattern, features of both hepato cellular and cholestatic injury are present (such as in cholestatic forms of viral hepatitis and many drug-induced liver diseases). The pattern of onset and prominence of symptoms can rapidly suggest a diagnosis, particularly if major risk factors are considered, such as the age and sex of the patient and a history of exposure or risk behaviors. Typical presenting symptoms of liver disease include jaundice, fatigue, itching, right-upper-quadrant pain, nausea, poor appetite, abdominal distention, and intestinal bleeding. At present, however, many patients are diagnosed with liver disease who have no symptoms and who have been found to have abnormalities in biochemical liver tests as a part of a routine physical examination or screening for blood donation or for insurance or employment. The wide availability of bat teries of liver tests makes it relatively simple to demonstrate the pres ence of liver injury as well as to rule it out in someone in whom liver disease is suspected. Evaluation of patients with liver disease should be directed at deter mining (1) the etiologic diagnosis, (2) disease severity (grading), and (3) disease stage (staging). Diagnosis should focus on the pattern of

TABLE 347-1 Liver Diseases Inherited hyperbilirubinemia Gilbert syndrome Crigler-Najjar syndrome, types I Liver involvement in systemic diseases Sarcoidosis Amyloidosis Glycogen storage diseases Celiac disease Tuberculosis Mycobacterium avium-intracellulare and II Dubin-Johnson syndrome Rotor syndrome Viral hepatitis Hepatitis A Hepatitis B Hepatitis C Hepatitis D Hepatitis E Others (Epstein-Barr virus infection Cholestatic syndromes Benign postoperative cholestasis Jaundice of sepsis Total parenteral nutrition–induced jaundice Cholestasis of pregnancy Cholangitis and cholecystitis Extrahepatic biliary obstruction [mononucleosis] herpesvirus, cytomegalovirus, adenovirus hepatitis) Cryptogenic hepatitis Immune and autoimmune liver diseases Primary biliary cholangitis Autoimmune hepatitis Sclerosing cholangitis Overlap syndromes Graft-versus-host disease Allograft rejection Genetic liver diseases a1 Antitrypsin deficiency Hemochromatosis Wilson disease Benign recurrent intrahepatic (stone, stricture, cancer) Biliary atresia Caroli disease Cryptosporidiosis Drug-induced liver disease Hepatocellular patterns (isoniazid, acetaminophen) Cholestatic patterns (methyltestosterone) Mixed patterns (sulfonamides, phenytoin) Micro- and macrovesicular steatosis PART 10 Disorders of the Gastrointestinal System (methotrexate, fialuridine) Vascular injury Sinusoidal obstruction syndrome Budd-Chiari syndrome Ischemic hepatitis Passive congestion Portal vein thrombosis Nodular regenerative hyperplasia Mass lesions Hepatocellular carcinoma Cholangiocarcinoma Adenoma Focal nodular hyperplasia Metastatic tumors Abscess Cysts Hemangioma cholestasis Progressive familial intrahepatic cholestasis, types I–III Others (galactosemia, tyrosinemia, cystic fibrosis, Niemann-Pickdisease, Gaucher’s disease) Alcohol-related liver disease Acute fatty liver Acute alcoholic hepatitis Laënnec cirrhosis Nonalcoholic fatty livera Steatosis Steatohepatitis Acute fatty liver of pregnancy aAlso known as metabolic dysfunction–associated steatotic liver disease (MASLD). disease presentation (hepatocellular, cholestatic, or mixed injury) as well as on the specific etiologic diagnosis. Grading refers to assessment of the severity or activity of disease—active or inactive as well as mild, moderate, or severe. Staging refers to estimation of the point in the course of the natural history of the disease, whether early or late; or precirrhotic, cirrhotic, or end-stage. This chapter introduces general, salient concepts in the evaluation of patients with liver disease that help lead to the diagnoses discussed in subsequent chapters. ■ ■CLINICAL HISTORY The clinical history should focus on the symptoms of liver disease— their nature, patterns of onset, and progression—and on potential risk factors for liver disease. The manifestations of liver disease include constitutional

symptoms such as fatigue, weakness, nausea, poor appe tite, and malaise and the more liver-specific symptoms of jaundice, dark urine, light stools, itching, abdominal pain, and bloating. Symp toms can also suggest the presence of cirrhosis, end-stage liver disease,

or complications of cirrhosis such as portal hypertension. Generally, the constellation of symptoms and their patterns of onset, rather than a specific symptom, point to an etiology. Fatigue is the most common and most characteristic symptom of liver disease. It is variously described as lethargy, weakness, listlessness, malaise, increased need for sleep, lack of stamina, and poor energy. The fatigue of liver disease typically arises after activity or exercise and is rarely present or severe after adequate rest; that is, it is “afternoon” rather than “morning” fatigue. Fatigue in liver disease is often intermit tent and variable in severity from hour to hour and day to day. In some patients, it may not be clear whether fatigue is due to the liver disease or due to other problems such as stress, anxiety, sleep disturbance, or a concurrent illness. Nausea occurs with more severe liver disease and may accompany fatigue or be provoked by smelling food odors or eating fatty foods. Vomiting can occur but is rarely persistent or prominent. Poor appetite with weight loss occurs frequently in acute liver disease but is rare in chronic disease except when cirrhosis is present and advanced. Diarrhea is uncommon in liver disease except with severe jaundice, in which a lack of bile acids reaching the intestine can lead to steatorrhea. Right-upper-quadrant discomfort or ache (“liver pain”) occurs in many liver diseases and is usually marked by tenderness over the liver area. The pain arises from stretching or irritation of Glisson’s capsule, which surrounds the liver and is rich in nerve endings. Severe pain is most typical of gallbladder disease, liver abscess, and severe sinusoidal obstruction syndrome (previously known as venoocclusive disease) but is also an occasional accompaniment of acute hepatitis. Itching occurs with acute liver disease, appearing early in obstruc tive jaundice (from biliary obstruction) or drug-induced cholestasis and somewhat later in hepatocellular disease (acute hepatitis). Itching also occurs in chronic liver diseases—typically the cholestatic forms such as primary biliary cholangitis and sclerosing cholangitis, in which it is often the presenting symptom, preceding the onset of jaundice. However, itching can occur in any liver disease, particularly once cir rhosis develops. Jaundice is the hallmark symptom of liver disease and perhaps the most reliable marker of severity. Patients usually report darkening of the urine before they notice scleral icterus. Jaundice is rarely detectable with a bilirubin level <43 μmol/L (2.5 mg/dL). With severe cholestasis, there will also be lightening of the color of the stools and steatorrhea. Jaundice without dark urine usually indicates indirect (unconjugated) hyperbilirubinemia and is typical of hemolytic anemia and the genetic disorders of bilirubin conjugation, the common and benign form being Gilbert syndrome and the rare and severe form being Crigler-Najjar syndrome. Gilbert syndrome affects up to 5% of the general popula tion; the jaundice in this condition is more noticeable after fasting and with stress. Major risk factors for liver disease that should be sought in the clini cal history include details of alcohol use, medication use (including herbal compounds, birth control pills, and over-the-counter medica tions), personal habits, sexual activity, travel, exposure to jaundiced or other high-risk persons, injection drug use, recent surgery, remote or recent transfusion of blood or blood products, occupation, accidental exposure to blood or needlestick, and familial history of liver disease. For assessing the risk of viral hepatitis, a careful history of sexual activity is of particular importance and should include the number of lifetime sexual partners and, for men, a history of having sex with men. Sexual exposure is a common mode of spread of hepatitis B and D but is uncommon for hepatitis C. A family history of hepatitis, liver disease, and liver cancer is also important. Maternal-infant transmis sion occurs with both hepatitis B and C. Vertical spread of hepatitis B can now be

prevented by passive and active immunization of the infant at birth. Additionally, antiviral therapy administered in the second or third trimester of pregnancy is now recommended for mothers with levels of hepatitis B virus DNA >200,000 IU/mL. Vertical spread of hepatitis C is uncommon, but there are no reliable means of preven tion. Transmission is more common among HIV-co-infected mothers and is also linked to prolonged and difficult labor and delivery, early rupture of membranes, internal fetal monitoring, and a high maternal

viral load. A history of injection drug use, even in the remote past, is of great importance in assessing the risk for hepatitis B, C, and D. Injection drug use is the single most common risk factor for hepatitis C. Transfusion with blood or blood products is no longer an important risk factor for acute viral hepatitis due to screening of blood products. However, blood transfusions received before the introduction of sensi tive enzyme immunoassays for antibody to hepatitis C virus in 1992 is an important risk factor for chronic hepatitis C. Blood transfusion before 1986, when screening for antibody to hepatitis B core antigen was introduced, is also a risk factor for hepatitis B. Travel to a develop ing area of the world, exposure to persons with jaundice, and exposure to young children in day-care centers are risk factors for hepatitis A. Tattooing and body piercing (for hepatitis B, C, and D) and eating shellfish (for hepatitis A) are frequently mentioned but are actually types of exposure that rarely lead to infection. Hepatitis E is one of the more common causes of jaundice in Asia and Africa but is uncommon in developed nations. In endemic areas, transmission is usually through exposure to fecally contaminated water. Non-travel-related (autochthonous) cases of hepatitis E have been described in developed countries, including the United States. These cases appear to be due to strains of hepatitis E virus that are endemic in swine and some wild animals (genotypes 3 and 4). While occasional cases are associated with eating raw or undercooked pork or game (deer and wild boars), most cases of hepatitis E occur without known exposure, predominantly in elderly men without typical risk factors for viral hepatitis. Hepatitis E infection can become chronic in immunosuppressed individuals (such as transplant recipients, patients receiving chemotherapy, or patients with HIV infection), in whom it presents with abnormal serum enzymes in the absence of markers of hepatitis B or C. A history of alcohol intake is important in assessing the cause of liver disease and in planning management and recommendations. In the United States, for example, at least 70% of adults drink alcohol to some degree, but significant alcohol intake is less common; in population-based surveys, only 5% of individuals have more than two drinks per day, the average drink representing 11–15 g of alcohol. Alco hol consumption associated with an increased rate of alcoholic liver disease is probably more than two drinks (22–30 g) per day in women and three drinks (33–45 g) in men. Most patients with alcoholic cir rhosis have a much higher daily intake and have drunk excessively for ≥10 years before onset of liver disease. In assessing alcohol intake, the history should also focus on whether alcohol abuse or dependence is present. Alcoholism is usually defined by the behavioral patterns and consequences of alcohol intake, not by the amount. Abuse is defined by a repetitive pattern of drinking alcohol that has adverse effects on social, family, occupational, or health status. Dependence is defined by alcohol-seeking behavior, despite its adverse effects. Many alcoholics demonstrate both dependence and abuse, and dependence is consid ered the more serious and advanced form of alcoholism. A clinically helpful approach to diagnosis of alcohol dependence and abuse is the use of the CAGE questionnaire (Table 347-2), which is recommended for all medical history-taking. Family history can be helpful in assessing liver disease. Familial causes of liver disease include Wilson disease; hemochromatosis and α1 antitrypsin deficiency; and the less common inherited pediatric liver diseases—that is, familial intrahepatic cholestasis, benign recur

rent intrahepatic cholestasis, and Alagille syndrome. Onset of severe TABLE 347-2 CAGE Questionsa ACRONYM QUESTION C Have you ever felt you ought to cut down on your drinking? A Have people annoyed you by criticizing your drinking? G Have you ever felt guilty or bad about your drinking? E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)? aOne “yes” response should raise suspicion of an alcohol use problem, and more than one is a strong indication of abuse or dependence.

liver disease in childhood or adolescence in conjunction with a family history of liver disease or neuropsychiatric disturbance should lead to investigation for Wilson disease. A family history of cirrhosis, diabetes, or endocrine failure and the appearance of liver disease in adulthood suggest hemochromatosis and should prompt investigation of iron status. Abnormal iron studies in adult patients warrant genotyping of the HFE gene for the C282Y and H63D mutations typical of genetic hemochromatosis. In children and adolescents with iron overload, other non-HFE causes of hemochromatosis should be sought. A family history of emphysema should lead to investigation of α1 antitrypsin levels and, if low, for protease inhibitor (Pi) genotype.

■ ■PHYSICAL EXAMINATION The physical examination rarely uncovers evidence of liver dysfunction in a patient without symptoms or abnormal laboratory findings, nor are most signs of liver disease specific to one diagnosis. Thus, the phys ical examination complements rather than replaces the need for other diagnostic approaches. In many patients, the physical examination is normal unless the disease is acute or severe and advanced. Neverthe less, the physical examination is important in that it can yield the first evidence of hepatic failure, portal hypertension, and liver decompen sation. In addition, the physical examination can reveal signs—related either to risk factors or to associated diseases or findings—that point to a specific diagnosis. Typical physical findings in liver disease are icterus, hepatomegaly, hepatic tenderness, splenomegaly, spider angiomata, palmar erythema, and skin excoriations. Signs of advanced disease include muscle wast ing, ascites, edema, dilated abdominal veins, hepatic fetor, asterixis, mental confusion, stupor, and coma. In male patients with cirrhosis, particularly that related to alcohol use, signs of hyperestrogenemia such as gynecomastia, testicular atrophy, and loss of male-pattern hair distribution may be found. CHAPTER 347 Icterus is best appreciated when the sclera is inspected under natu ral light. In fair-skinned individuals, a yellow tinge to the skin may be obvious. In dark-skinned individuals, examination of the mucous membranes below the tongue can demonstrate jaundice. Jaundice is rarely detectable if the serum bilirubin level is <43 μmol/L (2.5 mg/dL) but may remain detectable below this level during recovery from jaun dice (because of protein and tissue binding of conjugated bilirubin). Approach to the Patient with Liver Disease Spider angiomata and palmar erythema occur in both acute and chronic liver disease; these manifestations may be especially prominent in persons with cirrhosis but can develop in normal individuals and are frequently found during pregnancy. Spider angiomata are superficial, tortuous arterioles, and—unlike simple telangiectasias—typically fill from the center outward. Spider angiomata occur only on the arms, face, and upper torso; they can be pulsatile and may be difficult to detect in dark-skinned individuals. Hepatomegaly is not a very reliable sign of liver disease because of variability in the liver’s size and shape and the physical impediments to assessment of liver size by percussion and palpation. Marked hepato megaly is typical of cirrhosis, sinusoidal obstruction syndrome, infil trative disorders such as amyloidosis, metastatic or primary cancers of the liver, and alcoholic hepatitis. Careful assessment of the liver edge may also reveal unusual firmness, irregularity of the surface, or frank nodules. Perhaps the most reliable physical finding in

the liver exami nation is hepatic tenderness. Discomfort when the liver is touched or pressed upon should be carefully sought with percussive comparison of the right and left upper quadrants. Splenomegaly, which occurs in many medical conditions, can be a subtle but significant physical finding in chronic liver disease and suggests underlying cirrhosis. The availability of ultrasound (US) methods for assessment of the spleen allows confirmation of the physi cal finding. Signs of advanced liver disease include muscle wasting and weight loss as well as hepatomegaly, bruising, ascites, and edema. Ascites is best appreciated by attempts to detect shifting dullness by careful percussion. US examination will confirm the finding of ascites in equivocal cases. Peripheral edema can occur with or without ascites. In patients with advanced liver disease, other factors frequently contribute

to edema formation, including hypoalbuminemia, venous insuffi ciency, heart failure, and medications.

Hepatic failure is defined as the occurrence of signs or symptoms of hepatic encephalopathy in a person with severe acute or chronic liver disease. The first signs of hepatic encephalopathy can be subtle and nonspecific—change in sleep patterns, change in personality, irritabil ity, and mental dullness. Thereafter, confusion, disorientation, stupor, and eventually coma supervene. In acute liver failure, excitability and mania may be present. Physical findings include asterixis and flapping tremors of the body and tongue. Fetor hepaticus refers to the slightly sweet, ammoniacal odor that can develop in patients with liver failure, particularly if there is portal-venous shunting of blood around the liver. Other causes of coma and disorientation should be excluded, mainly electrolyte imbalances, sedative use, and renal or respiratory failure. The appearance of hepatic encephalopathy during acute hepatitis is the major criterion for diagnosis of acute liver failure and indicates a poor prognosis. In chronic liver disease, encephalopathy is usually triggered by a medical complication such as gastrointestinal bleeding, overdiure sis, uremia, dehydration, electrolyte imbalance, infection, constipation, or use of narcotic analgesics. A helpful measure of hepatic encephalopathy is a careful mental status examination and use of the trail-making test, which consists of a series of 25 numbered circles that the patient is asked to connect as rapidly as possible using a pencil. The normal range for the connectthe-dot test is 15–30 s; it is considerably longer in patients with early hepatic encephalopathy. Other tests include drawing of abstract objects or comparison of a signature to previous examples. More sophisticated testing—for example, with electroencephalography and visual evoked potentials—can detect mild forms of encephalopathy but are rarely clinically useful. PART 10 Disorders of the Gastrointestinal System Other signs of advanced liver disease include umbilical hernia from ascites, hydrothorax, prominent veins over the abdomen, and caput medusa, a condition that consists of collateral veins radiating from the umbilicus and results from recanulation of the umbilical vein. Wid ened pulse pressure and signs of a hyperdynamic circulation can occur in patients with cirrhosis as a result of fluid and sodium retention, increased cardiac output, and reduced peripheral resistance. Patients with long-standing cirrhosis and portal hypertension are prone to develop the hepatopulmonary syndrome, which is defined by the triad of liver disease, hypoxemia, and pulmonary arteriovenous shunting. The hepatopulmonary syndrome is characterized by platypnea and orthodeoxia: shortness of breath and oxygen desaturation that occur paradoxically upon the assumption of an upright position. Measure ment of oxygen saturation by pulse oximetry is a reliable screening test for hepatopulmonary syndrome. Several skin disorders and changes are common in liver disease. Hyperpigmentation is typical of advanced chronic cholestatic diseases such as primary biliary

cholangitis and sclerosing cholangitis. In these same conditions, xanthelasma and tendon xanthomata occur as a result of retention and high serum levels of lipids and cholesterol. Slate-gray pigmentation of the skin is also seen with hemochromatosis if iron levels are high for a prolonged period. Mucocutaneous vasculitis with palpable purpura, especially on the lower extremities, is typical of cryoglobulinemia of chronic hepatitis C but can also occur in chronic hepatitis B. Some physical signs point to specific liver diseases. Kayser-Fleischer rings occur in Wilson disease and consist of a golden-brown copper pigment deposited in Descemet's membrane at the periphery of the cornea; they are best seen by slit-lamp examination. Dupuytren con tracture and parotid enlargement are suggestive of alcohol use disorder and alcohol-related liver disease. In metastatic liver disease or primary hepatocellular carcinoma (HCC), signs of cachexia and wasting as well as firm hepatomegaly and a hepatic bruit may be prominent. ■ ■DIAGNOSIS OF LIVER DISEASE The key diagnostic tests of major causes of acute and chronic liver dis ease are outlined in Table 347-3, and an algorithm for evaluation of the patient with suspected liver disease is shown in Fig. 347-1. Specifics of diagnosis are discussed in later chapters. The most common causes of

TABLE 347-3 Important Diagnostic Tests in Common Liver Diseases DISEASE DIAGNOSTIC TEST Hepatitis A Anti-HAV IgM Hepatitis B Acute HBsAg and anti-HBc IgM Chronic HBsAg and HBeAg and/or HBV DNA Hepatitis C Anti-HCV and HCV RNA Hepatitis D (delta) HBsAg and anti-HDV Hepatitis E Anti-HEV IgM and HEV RNA Autoimmune hepatitis ANA or SMA, elevated IgG levels, and compatible histology Primary biliary cholangitis Mitochondrial antibody, elevated IgM levels, and compatible histology Primary sclerosing cholangitis P-ANCA, cholangiography Drug-induced liver disease History of drug ingestion Alcohol-related liver disease History of excessive alcohol intake and compatible histology Nonalcoholic steatohepatitisa Ultrasound or CT evidence of fatty liver and compatible histology a1 Antitrypsin disease Reduced α1 antitrypsin levels, phenotype PiZZ or PiSZ Wilson disease Decreased serum ceruloplasmin and increased urinary copper; increased hepatic copper level Hemochromatosis Elevated iron saturation and serum ferritin; genetic testing for HFE gene mutations Hepatocellular cancer Elevated α-fetoprotein level (to >500 ng/mL); ultrasound or CT image of mass aAlso known as metabolic dysfunction–associated steatohepatitis (MASH). Abbreviations: ANA, antinuclear antibody; anti-HBc, antibody to hepatitis B core (antigen); CT, computed tomography; HAV, HBV, HCV, HDV, HEV, hepatitis A, B, C, D, E virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; P-ANCA, peripheral antineutrophil cytoplasmic antibody; SMA, smooth-muscle antibody. acute liver disease are viral hepatitis (particularly hepatitis A, B, and C), drug-induced liver injury, cholangitis, and alcohol-related liver disease. Liver biopsy usually is not needed for the diagnosis and management of acute liver disease, exceptions being situations where the diagnosis remains unclear despite thorough clinical and laboratory investigation. Liver biopsy can be helpful in diagnosing drug-induced liver disease and acute alcoholic hepatitis. The most common causes of chronic liver disease, in general order of frequency, are chronic hepatitis C, alcoholic liver disease, nonal coholic steatohepatitis (also called metabolic dysfunction–associated steatohepatitis), chronic hepatitis B, autoimmune hepatitis, sclerosing cholangitis, primary biliary cholangitis, hemochromatosis, and Wilson disease. Hepatitis E virus is a rare cause of chronic hepatitis, with cases occurring mostly in persons who are immunosuppressed or immuno deficient. Strict diagnostic criteria have not been developed for most liver diseases, but liver biopsy plays an important role in the diagnosis of autoimmune hepatitis, primary biliary cholangitis, nonalcoholic and alcoholic steatohepatitis, and Wilson disease (with a quantitative hepatic copper level in the last instance). Laboratory Testing Diagnosis of liver

disease is greatly aided by the availability of reliable and sensitive tests of liver injury and func tion. A typical battery of blood tests used for initial assessment of liver disease includes measurement of levels of serum alanine (ALT) and aspartate (AST) aminotransferases, alkaline phosphatase (AlkP), direct and total serum bilirubin and albumin, and prothrombin time. The pattern of abnormalities generally points to hepatocellular versus cholestatic liver disease and helps determine whether the disease is acute or chronic and whether cirrhosis and hepatic failure are present. Based on these results, further testing over time may be necessary. Other laboratory tests may be helpful, such as γ-glutamyl transpepti dase (γGT) to define whether AlkP elevations are due to liver disease; hepatitis serology to define the type of viral hepatitis; and autoimmune markers to diagnose primary biliary cholangitis (antimitochondrial

Suspected liver disease Abnormal liver tests Acute <6 months Chronic

> 6 months Hepatitic: ⇑⇑ALT Mixed: ↑ALT, ↑AlkP Hepatitic: ⇑⇑ALT Mixed: ↑ALT, ↑AlkP Cholestatic: ⇑⇑AlkP, ⇑⇑gGT, ↑ALT Diagnostic evaluation

1. IgM Anti-HAV
2. HBsAg
3. IgM Anti-HBc
4. Anti-HCV
5. ANA, SMA
6. Monospot, heterophile
7. Ceruloplasmin
8. Alcohol history
9. Drug history Diagnostic evaluation
10. HBsAg
11. Anti-HCV
12. Fe saturation, ferritin
13. Ceruloplasmin
14. α1AT
15. ANA, SMA
16. Ultrasound
17. Alcohol history Diagnostic evaluation
18. AMA
19. Drug history
20. Ultrasound/MRI
21. MRCP/ERCP Liver biopsy in acute liver disease: Reserved for patients in whom the diagnosis remains unclear despite medical evaluation Liver biopsy in chronic liver disease: Often valuable for diagnosis as well as staging and grading liver disease FIGURE 347-1 Algorithm for evaluation of abnormal liver tests. For patients with suspected liver disease, an appropriate approach to evaluation is initial routine liver testing—for example, measurement of serum bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AlkP). These results (sometimes complemented by testing of γ-glutamyl transpeptidase [γGT]) will establish whether the

pattern of abnormalities is hepatic, cholestatic, or mixed. In addition, the duration of symptoms or abnormalities will indicate whether the disease is acute or chronic. If the disease is acute and if history, laboratory tests, and imaging studies do not reveal a diagnosis, liver biopsy is appropriate to help establish the diagnosis. If the disease is chronic, liver biopsy can be helpful not only for diagnosis but also for grading of the activity and staging the progression of disease. This approach is generally applicable to patients without immune deficiency. In patients with HIV infection or recipients of bone marrow or solid organ transplants, the diagnostic evaluation should also include evaluation for opportunistic infections (e.g., with adenovirus, cytomegalovirus, Coccidioides, hepatitis E virus) as well as for vascular and immunologic conditions (venoocclusive disease, graft-versus-host disease). α1AT, α1 antitrypsin; AMA, antimitochondrial antibody; ANA, antinuclear antibody; anti-HBc, antibody to hepatitis B core (antigen); ERCP, endoscopic retrograde cholangiopancreatography; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MRCP, magnetic resonance cholangiopancreatography; P-ANCA, peripheral antineutrophil cytoplasmic antibody; SMA, smoothmuscle antibody. TABLE 347-4 Diagnostic Tests to Assess Liver Fat IMAGING MODALITY ADVANTAGES DISADVANTAGES CLINICAL UTILITY Ultrasound No radiation Widely available Transient elastography with controlled attenuation parameter No radiation Point-of-care assessment of liver fat Provides semiquantitative assessment of fat severity Computed tomography Rapid assessment Non–operator dependent Quantitative assessment of fat severity Magnetic resonance imaging– proton density fat fraction Direct assessment of liver fat Highly sensitive and specific

antibody), sclerosing cholangitis (peripheral antineutro phil cytoplasmic antibody), and autoimmune hepatitis (antinuclear, smooth-muscle, and liver-kidney micro somal antibody). A simple delineation of laboratory abnormalities and common liver diseases is given in Table 347-3.

The use and interpretation of liver function tests are summarized in Chap. 348. Diagnostic Imaging Great advances have been made in hepatobiliary imaging, although no method is adequately accurate in demonstrating underlying cir rhosis in its early stages. Of the many modalities avail able for imaging the liver, US, computed tomography (CT), and magnetic resonance imaging (MRI) are the most commonly employed and are complementary to one another. In general, US and CT are highly sensitive for detecting biliary duct dilation and are the first-line options for investigating cases of suspected obstructive jaundice. All three modalities can detect a fatty liver, which appears bright on imaging studies. Modifications of CT and MRI can be used to quantify liver fat, and this information may ultimately be valuable in monitoring response to therapy in patients with fatty liver disease. Advantages, disadvantages, and clinical utility of each modality are presented in Table 347-4. Magnetic reso nance cholangiopancreatography (MRCP) and endo scopic retrograde cholangiopancreatography (ERCP) are the procedures of choice for visualization of the biliary tree. MRCP offers several advantages over ERCP: there is no need for contrast media or ionizing radiation, images can be acquired faster, the procedure is less operator dependent, and it carries no risk of pancreatitis. MRCP is superior to US and CT for detecting choledocholithia sis but is less specific. MRCP is useful in the diagnosis of bile duct obstruction and congenital biliary abnormali ties, but ERCP is considered more valuable in evaluating ampullary lesions and primary sclerosing cholangitis. ERCP permits biopsy, direct visualization of the ampulla and common bile duct, and intraductal ultrasonography and brushings for cytologic evaluation of malignancy. It also provides

several therapeutic options in patients with obstructive jaundice, such as sphincterotomy, stone extraction, and placement of nasobiliary catheters and biliary stents. Cholestatic: ⇑⇑AlkP, ⇑⇑gGT, ↑ALT Diagnostic evaluation

1. Drug history
2. AMA
3. P-ANCA
4. Ultrasound
5. MRCP/ERCP CHAPTER 347 Approach to the Patient with Liver Disease Doppler US and MRI are used to assess hepatic vasculature and hemodynamics and to monitor surgi cally or radiologically placed vascular shunts, including Operator dependent Imprecise qualitative assessment of fat severity, particularly mild steatosis Initial screening test for suspected liver fat Requires special software No reliable cutoff for diagnosis of liver fat Imprecise qualitative assessment of fat severity Alternate screening test for suspected liver fat if available Requires radiation Quantification of fat requires specific protocols Imprecise quantitative assessment of fat severity, particularly mild steatosis Not recommended for clinical assessment of liver fat due to need for radiation exposure and low sensitivity for mild fat Relatively limited accessibility Test of choice for quantitative assessment of liver fat if available

transjugular intrahepatic portosystemic shunts. Multidetector or spiral CT and MRI with contrast enhancement are the procedures of choice for the identification and evaluation of hepatic masses, the staging of liver tumors, and preoperative assessment. With regard to mass lesions, the sensitivity of hepatic imaging continues to increase; unfortunately, specificity remains a problem, and often two and sometimes three studies are needed before a diagnosis can be reached. An emerging imaging modality for the investigation of hepatic lesions is contrastenhanced US. This procedure permits enhancement of liver lesions in a similar fashion as contrast-enhanced, cross-sectional CT or MRI. Major advantages are real-time assessment of liver perfusion through out the vascular phases without risk of nephrotoxicity and radiation exposure. Other advantages are its widespread availability and lower cost. Limitations include body habitus of the patient and skill of the operator.

US is the recommended modality for HCC screening. Contrastenhanced US, CT, and MRI are appropriate for further investigation of lesions detected on screening US. The American College of Radi ologists has developed a Liver Imaging Reporting and Data System (LI-RADS) to standardize the reporting and data collection of CT, MRI, and contrast-enhanced US imaging for HCC. This system allows for more consistent reporting and reduces imaging interpretation vari ability and errors. Recently, several US-based elastographic techniques have been developed and approved for the measurement of hepatic stiffness, providing an indirect assessment of fibrosis and cirrhosis. The most commonly used approaches in clinical practice include transient elastography, acoustic radiation force impulse imaging, shear-wave elasticity imaging, and supersonic shear imaging. These techniques can eliminate the need for liver biopsy if the only indication for the test is the assessment of disease stage. Magnetic resonance elastography is more sensitive than US elastography but is also more expensive and requires advanced scheduling and special equipment. Finally, interven tional radiologic techniques allow for the biopsy of solitary lesions, the radiofrequency ablation and chemoembolization of cancerous lesions, the insertion of drains into

hepatic abscesses, the measurement of portal pressure, and the creation of vascular shunts in patients with portal hypertension. Which modality to use depends on factors such as availability, cost, and experience of the radiologist with each technique. PART 10 Disorders of the Gastrointestinal System Liver Biopsy Liver biopsy remains the gold standard in the evalu ation of patients with liver disease, particularly chronic liver disease. Liver biopsy is necessary for diagnosis in selected instances but is more often useful for assessment of the severity (grade) and stage of liver damage, prediction of prognosis, and monitoring of the response to treatment. The size of the liver biopsy sample is an important determinant of reliability; a length of 1.5–2 cm with 10 portal tracts is necessary for accurate assessment of fibrosis. Because liver biopsy is an invasive procedure and not without complications, it should be used only when it will contribute materially to decisions about man agement and therapy. In the future, noninvasive means of assessing disease activity (batteries of blood tests) and fibrosis (elastography and fibrosis markers) may replace liver biopsy for the staging and grading of disease. ■ ■GRADING AND STAGING OF LIVER DISEASE Grading refers to an assessment of the severity or activity of liver dis ease, whether acute or chronic; active or inactive; and mild, moderate, or severe. Liver biopsy is the most accurate means of assessing severity, particularly in chronic liver disease. Serum aminotransferase levels serve as convenient and noninvasive markers for disease activity but do not always reliably reflect disease severity. Thus, normal serum amino transferase levels in patients with hepatitis B surface antigen in serum may indicate the inactive carrier state or may reflect mild chronic hepa titis B or hepatitis B with fluctuating disease activity. Serum testing for hepatitis B e antigen and hepatitis B virus DNA can help sort out these different patterns, but these markers can also fluctuate and change over time. Similarly, in chronic hepatitis C, serum aminotransferase levels can be normal despite moderate disease activity. Finally, in both

alcoholic and nonalcoholic steatohepatitis, aminotransferase levels are quite unreliable in reflecting severity. In these conditions, liver biopsy is helpful in guiding management and identifying appropriate therapy, particularly if treatment is difficult, prolonged, and expensive. Of the several well-verified numerical scales for histologic grading of chronic liver disease, the most commonly used are the METAVIR and the his tology activity index. Liver biopsy is also the most accurate means of assessing stage of disease as early or advanced and as precirrhotic or cirrhotic. Staging of disease pertains largely to chronic liver diseases in which progression to cirrhosis and end-stage disease can occur but may require years or decades. Clinical features, biochemical tests, and hepatic imaging stud ies are helpful in assessing stage but generally become abnormal only in the middle to late stages of cirrhosis. Noninvasive tests that suggest advanced fibrosis include mild elevations of bilirubin, prolongation of prothrombin time, slight decreases in serum albumin, and mild thrombocytopenia (which is often the first indication of worsen ing fibrosis). Combinations of blood test results that include clinical features, routine laboratory tests, and special laboratory tests such as serum proteins or small molecules that are affected by or involved with fibrogenesis have been used to create models for predicting advanced liver disease, but these models are not reliable enough to use on a regular basis or for repeated measures and only separate advanced from early disease (Table 347-5). Recently, elastography and nonin vasive breath tests using 13C-labeled compounds have been proposed as a means of detecting early stages of fibrosis and liver dysfunction, but their reliability and reproducibility remain to be proven. A major limitation of noninvasive markers is that they can be affected by disease activity. Even elastography is limited in this regard, in that it measures liver stiffness, not fibrosis per se, and can be affected by inflammation, edema, hepatocyte necrosis, and intrasinusoidal cellularity (inflamma tory,

malignant, or sickled cells). Thus, at present, mild to moderate stages of hepatic fibrosis are detectable only by liver biopsy. In the assessment of stage, the degree of fibrosis is usually used as the quanti tative measure. The amount of fibrosis is generally staged on a scale of 0 to 4+ (METAVIR scale) or 0 to 6+ (Ishak scale). The importance of staging relates primarily to prognosis, recommendation of therapy, and optimal management to prevent complications of chronic liver disease. Patients with cirrhosis are candidates for screening and surveillance for esophageal varices and HCC. Patients without advanced fibrosis need not undergo screening. Once cirrhosis develops, other scoring systems are employed to assess compensated versus decompensated disease and prognosis. The first staging system used for this purpose was the modified Child-Pugh TABLE 347-5 Selected Noninvasive Methods of Assessing Hepatic Fibrosis and Cirrhosis ADVANCED FIBROSIS CIRRHOSIS METHOD PARAMETERS APRI AST, platelet count

> 1 1.5 (1–2) ELF Age, hyaluronic acid, MMP-3, TIMP-1 7.7 9.3 FIB-4 Age, AST, ALT, platelet count 1.45 3.25 Fibro testa Haptoglobin, α2-macroglobulin, apolipoprotein A1, γGT, total bilirubin 0.45 0.63 TE Measures speed of a shear wave generated by vibration through liver tissue 7.3 kPa 15 kPa (9–26.5 kPa) ARFI Measures speed of shear wave generated by acoustic radiation force through liver tissue 1.3 m/s 1.87 m/s aPatented models. Note: The cut points presented in the table were mostly derived from patients with chronic hepatitis C. The cut points for the noninvasive models and tests presented in the table vary among different liver diseases and among patients with the same disease among different populations. Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio; ARFI, acoustic radiation force imaging; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis panel; γGT, γ-glutamyl transpeptidase; MMP-3, metalloproteinase-3; TIMP-1, tissue inhibitor of metalloproteinase-1; TE, transient elastography.

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